

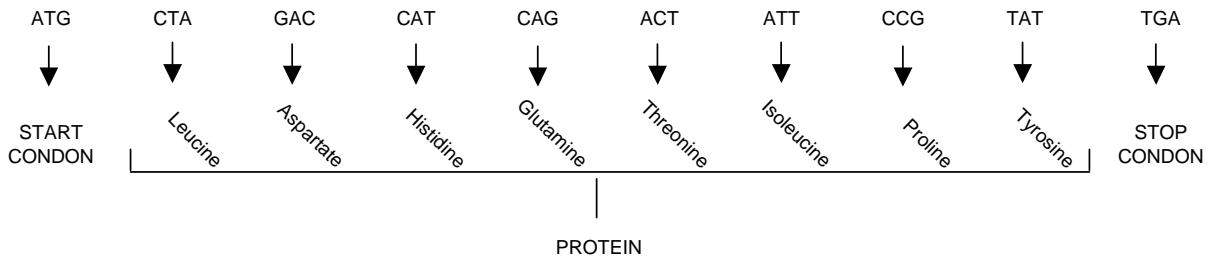
Genetics Primer

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How is the gene read?

The body has a very complex method for reading the gene letter sequence and converting it into a protein or enzyme. Proteins and enzymes are composed of a set of twenty different amino acids. Each protein has a unique sequence of amino acids bound together in a long string. But how does the text of the gene get converted into the amino acid string called a protein? All genes begin with the same three letters (i.e. ATG). From this initiator, the letters of the gene are read in sets of threes called codons. There are a total of 64 possible codons, each of which signifies a different amino acid. There are also three stop codons which signal the end of the gene (i.e. TAA, TAG, or TGA).

Using the short gene sequence from above, the figure below illustrates the method by which the DNA is read:



As the cellular machinery for reading the DNA moves along the strand of DNA, it reads the codons and translates that message into the corresponding amino acid. Since there are 64 possible codons but only 20 amino acids, most amino acids are coded by several different codons. For example, the amino acid isoleucine is coded by ATT, ATC, and ATA. Each amino acid is bound to the next in a stepwise fashion creating a long string of amino acids until the end of the gene (stop codon) is reached.

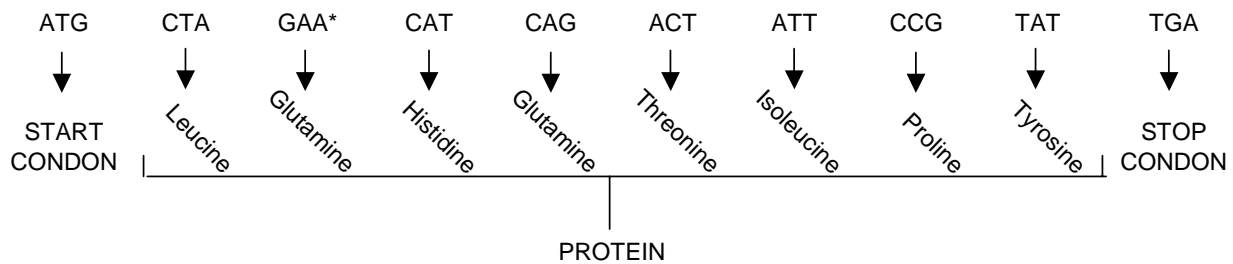
What is a mutation?

A mutation is an alteration in the letter sequence of a gene which causes the gene product, a protein or enzyme, to be manufactured incorrectly. When a protein is made improperly, it is usually ineffective and thus cannot perform its intended function. This lack of function often leads to disease. This is analogous to a typographical error on a single page of text in the 46-volume set of encyclopedias.

Are all mutations alike?

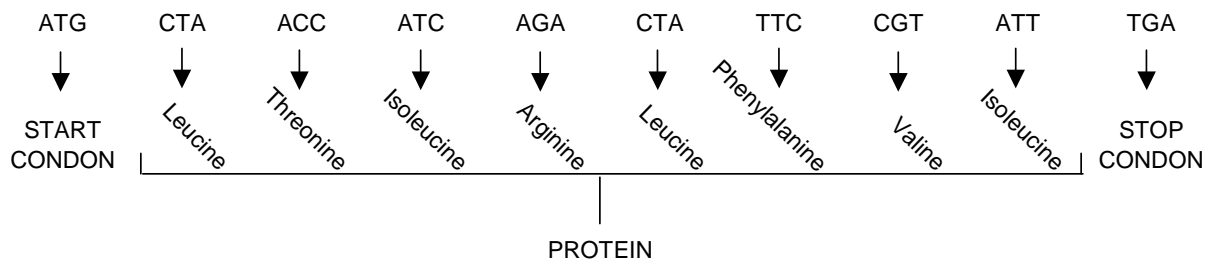
There are several different types of mutation which can alter a gene. First, there is the point mutation. This is the most common form. This type of mutation changes a single letter in the gene text. This typographical error results in the substitution

of one amino acid for another in the protein. Using the letter sequence from above, a point mutation has been introduced into the gene sequence below.

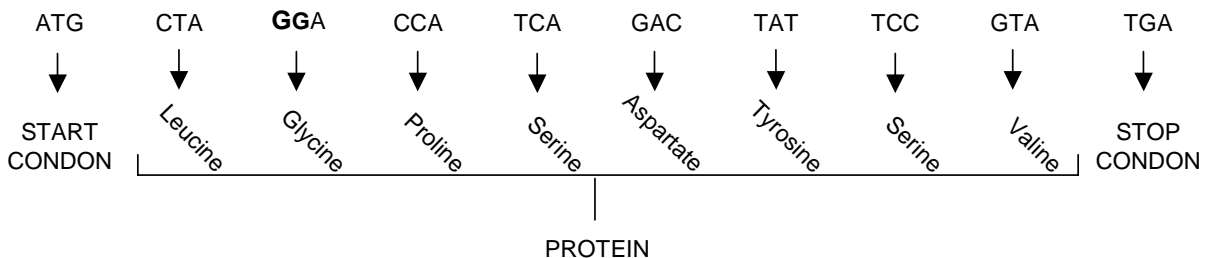


The mutation is marked by an asterisk in codon number 3. This substitution changes a C to an A. This alters the codon so that it no longer designates aspartate (codon GAC), but rather specifies glutamine (GAA). Most mutations of this type change a single amino acid within the protein, leaving the rest of the protein unaffected. The protein is usually manufactured, but often lacks proper function due to the incorrect placement of one amino acid.

A second type of mutation is called a deletion. Deletions may be large or small. Some deletions result in the loss of a single letter in the gene, while others may encompass many hundreds or thousands of letters. When some of the gene code is deleted, the protein often cannot be manufactured at all. The figure below illustrates a single letter deletion in codon three. The original codon 3 was GAC. In this example, the G has been deleted so the codon now reads ACC. This deletion shifts all the other letters forward in the sequence and disrupts the normal reading frame of the gene. As a result, the amino acids incorporated into the protein after the deletion are incorrect. This type of mutation often results in a non-functional protein.



A third form of mutation is called an insertion. As the name implies, an insertion adds extra letters to the text of the gene. Like the deletion mutation, this type may be small (a single letter insertion) or large (many hundreds or thousands of letters).



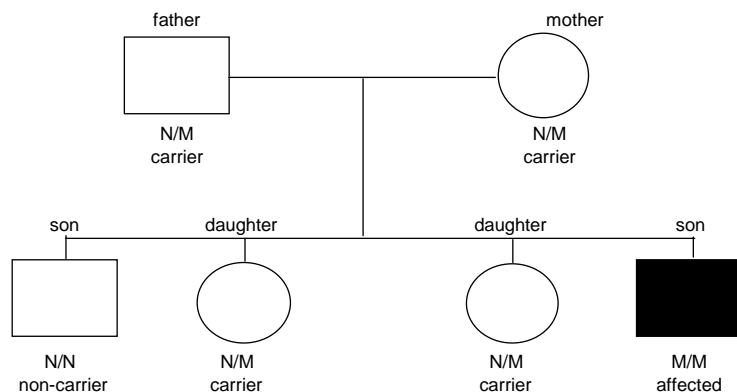
The end result, though, is the same as a deletion mutation: the protein is manufactured improperly, if at all. As an example, the sequence below has a G insertion in codon 3 (denoted by the outlined letter G). This insertion changes the third codon from GAC to GGA and substitutes glycine for aspartate in the protein. In addition, this insertion causes the reading frame to shift so that all subsequent amino acids are incorrect.

If I carry a mutation, why am I not sick?

Most of the genetic diseases we treat at the Clinic for Special Children are **recessive**. For a recessive genetic disease, both parents are “carriers” of a silent mutation. The mutation is silent in that there is no clinical consequence in being a carrier. Recall that each cell in the body has two copies of every gene, one inherited from the father and one from the mother. The carrier has one version of the gene which has mutation, while the other copy is normal. The normal copy is able to “mask” the presence of the mutant copy by providing the cells of the body with enough protein to function normally. However, when both copies of a gene contain a mutation, there is no normal protein produced. This leads to disease.

In the diagram below, the N represents the normal gene sequence and the M represents the mutant gene sequence. The diagram shows that, on average, one out of four children (25%) will inherit two copies of the abnormal gene and, thus, develop the disease. In addition, three out of four children will be unaffected by the disease, but, on average, two of these three will be carriers. The probability of having an affected child remains the same regardless of the number of affected or unaffected children already born to the couple.

A recessive genetic disease occurs in a child only if **both** parents carry a mutation in the same gene. This circumstance is usually rare. However, in plain (Amish)



communities, the incidence of **consanguineous** marriages is much higher than the general population. A consanguineous marriage is the union of two individuals who are genetically related. A consanguineous union may be a relatively close relationship (e.g. second cousins) or it may be more distant (e.g. sixth cousins). Due to the relatively small number of Mennonite and Amish founders and the lack of migration into the group over the past two centuries, most contemporary Mennonite and Amish individuals are related to their spouses. The closer the relationship between these two individuals, the greater is the probability that they will produce offspring with a genetic disease.

How can mutations be detected?

Once a mutation has been identified in a gene, a specific test can be designed to identify individuals who carry that mutation. The Clinic for Special Children offers genetic testing for carrier status for several inherited diseases, namely maple syrup disease (MSD), glutaric aciduria, type 1 (GA1), medium - chain acyl-CoA dehydrogenase deficiency (MCADD), glycogen storage disease, type 6 (GSDVI), pyruvate kinase deficiency (PKD), congenital nephritic syndrome (NPHS1), Byler disease (FIC1), Hirschsprung disease (HSCR), and Crigler-Najjar syndrome, type 1 (CNI). For each disorder, the test performed identifies a single mutation in the gene (namely Y393N for MSD, A421V for GA1, K304E for MCADD, IVS13+1G for GSDVI, R479H for PKD, 1481delC for NPHS1, G308V for FIC1, W276C for HSCR, and Y74X for CNI). Currently, research indicates that a single gene mutation for each disorder is found among the Mennonite and Amish populations of Lancaster County, PA. These tests do not detect other mutations within these genes which may cause disease.

DDC Clinic for Special Needs Children provides testing for prolidase deficiency through the laboratory of Dr. Hal Scofield at the Oklahoma Medical Research Foundation.