The Genomics Era: the Future of Genetics in Medicine

Errors in replication: Reference Sheet

When DNA is copied, over and over again in cell division, errors will inevitably be introduced. We call these errors in replication. A replication error can affect a single DNA base, several bases or sometimes larger chromosome regions.

Not all the errors introduced into the genome are pathogenic, or disease-causing. Indeed, as we discussed in week one, genomic variation is often completely normal and is what drives evolution and makes us unique. Whether a replication error results in disease depends on its size, its position and its effect on protein production.

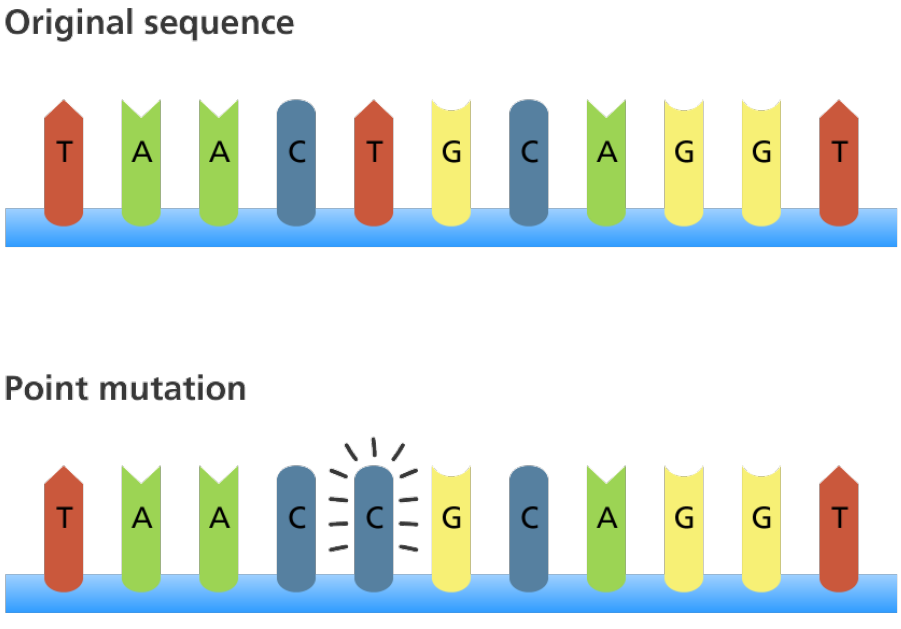
When we talk about gene mutations, we generally group them into point mutations or insertions / deletions.

Point mutations involve the substitution of a single base and can cause

A) synonymous,

B) nonsynonymous or

C) stop gain mutations.



Where there is a **synonymous change** there is a change in the base but it results in the same amino acid being encoded.

For example:

normal	T	H	E	C	A	T	W	A	S	F	A	T	
synonymous	T	H	E	K	A	T	W	A	S	F	A	T	

Although synonymous changes often don't cause disease, if they occur at one of the essential splice sites, which dictate how the introns are removed during protein production, they can be pathogenic.

A nonsynonymous change (also known as a missense mutation) is where a change in one DNA base pair causes a different amino acid to be substituted in the protein made by the gene:

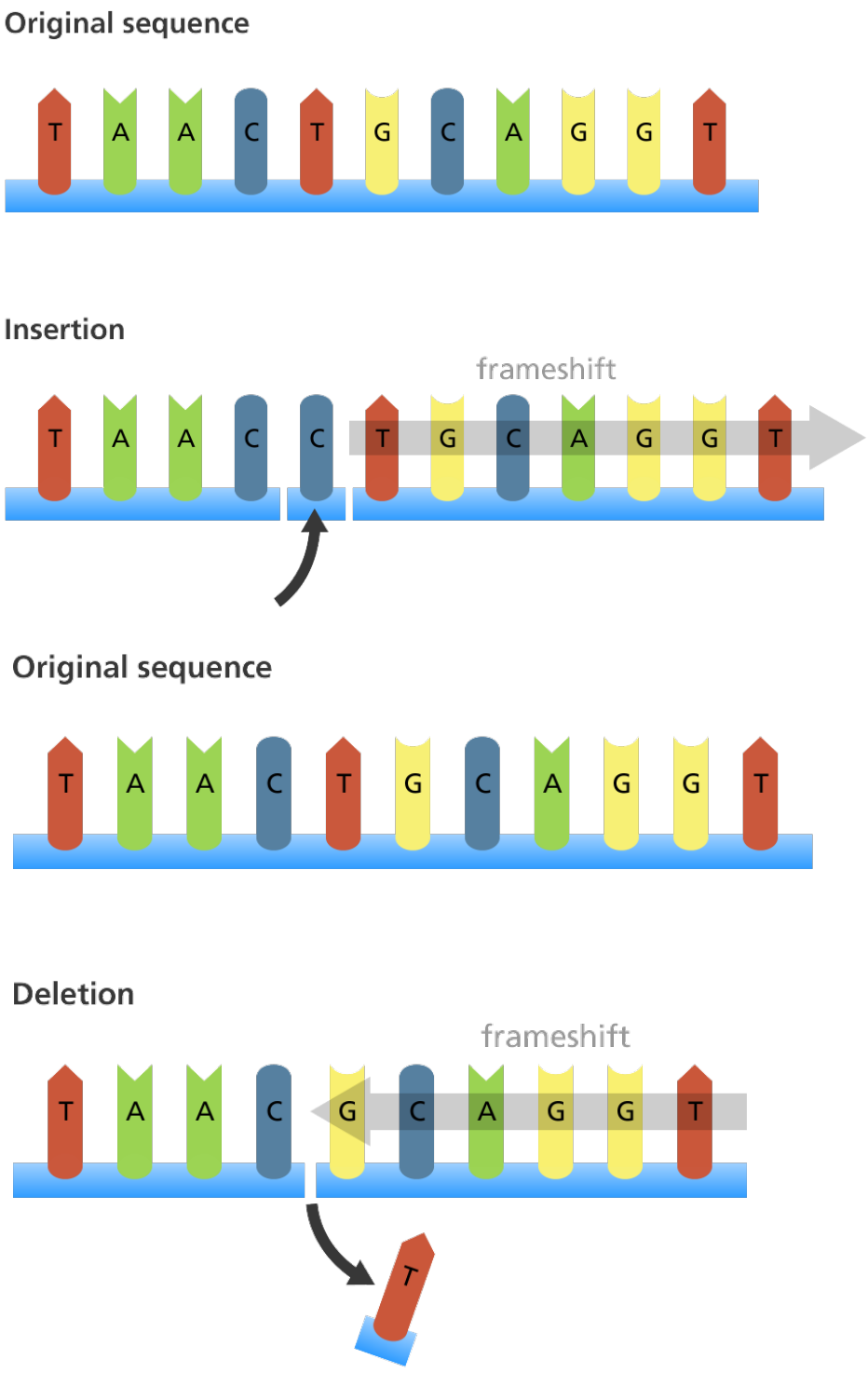
normal	T	H	E	C	A	T	W	A	S	F	A	T	
nonsynonymous	T	H	E	B	A	T	W	A	S	F	A	T	

The protein resulting from the nonsynonymous change will therefore have one different amino acid incorporated which, depending upon how vital that amino acid is to the protein structure and function, may be pathogenic.

A **stop gain** or **nonsense** mutation is where the altered DNA sequence prematurely tells the cell to stop building the protein. This means that the protein is shorter than it should be and may either be destroyed by the cell or may not function properly:

normal	T	H	E	C	A	T	W	A	S	F	A	T	
stop gain	T	H	E	F	A	T							

Insertions and deletions change the number of bases in a gene.



One or many bases may be inserted or deleted. If the number of bases inserted or deleted is not a multiple of three (the size of the codon) then the reading frame of the gene will be disrupted. This usually results in a shortened, abnormal protein which may or may not be destroyed by the cell:

normal	T	H	E	C	A	T	W	A	S	F	A	T
frameshifting del	T	H	E	A	T	W	A	S	F	A	T	

DELETION OF C

If the number of bases inserted or deleted is a multiple of three, then the insertion or deletion will not alter the reading frame and may be less deleterious:

normal	T	H	E	C	A	T	W	A	S	F	A	T
in-frame insertion	T	H	E	B	I	G	C	A	T	W	A	S