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Genetics Topic Assignment
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December 9, 2022

Cystic Fibrosis… a Deletion Causing Death

Nucleotides are essentially the building blocks of the earth and even the smallest changes may carry some of the most severe consequences. These nucleotides are created through the combination of one of the four nitrogenous bases: Adenine, Cytosine, Guanine, Thymine, or Uracil, a sugar, and a phosphate group. When these three pieces combine, nucleotides can be created, and given the ability to combine with other nucleotides, to create the building blocks of life, both DNA (utilizing the deoxyribose sugar), and RNA (utilizing the ribose sugar). When formed, the nucleotides bind in groups of three, called amino acids. When the amino acids are read together through the reading frame, they can express certain functions. These functions are what makes life on earth possible, continuously happening in all of life right now. But, when these amino acids, or even a single nucleotide, begin to encounter a mutation, some of the most life-threatening diseases, as well as other beneficial abilities or advantages can be brought into the preverbal picture.

There are quite a few variations of mutations that occur at a decent rate within everyday life. Substitution replaces one nucleotide base with another, an insertion adds at least one nucleotide, and a deletion resulting with one of more nucleotides being dropped from the sequence. each of them alters the effectiveness and accuracy of the reading frame. Deletion mutations are the most dangerous of the three due to it totally altering all the amino acid sequences that come after the mutation. Even if just one nucleotide is absent within the long line of amino acids, all the following would be read incorrectly, the wrong proteins could be read directly changing the desired function of the sequence. With so many lines of genetic code someone would assume that this would be happening way too often, and that life would be entirely left up to chance, but thanks to gene regulation this scary thought has been greatly mitigated. Unfortunately, these deletion mutations do still find a way through and past the gene regulation stages within organic life and continue to alter life and change the way we live. One of

the biggest examples, that accurately show what effects a simple deletion of a few nucleotides can have been the disease, cystic fibrosis.

The cystic fibrosis disease is an autosomal, monogenetic disorder which causes a stoppage of air reaching the lungs from a rapid buildup of mucus. This disease is the most common chronic lung diseases recorded and affects children typically but has been seen in some adults. Recorded for the first time close to a century ago by Dorothy Andersen in 1938 within his experiment on malnutrition. It took almost another sixty years for scientists in the modern day to find the true cause of this chronic disease. Cystic fibrosis is a result of a mutation in the cystic fibrosis transmembrane regulator gene (CFTR) which is mainly responsible to keep the salt and water levels within human lungs at a stasis, but when working incorrectly the CFTR allows for the salt to be moved in and around the human body. Thus, the salty build up leads to the mucus entering the lungs and blocking respiration from occurring.

The CFTR main purpose as a chloride ion channel is to maintain anion flow through itself to allow tissues called epithelia to function properly. Epithelia are spread throughout the body and cover most surfaces letting human have a form of absorption from the outside world, filtration of unnecessary or wanted compounds, and basic sensory reception from the body itself and the outside world. Needless to say, the cystic fibrosis transmembrane regulator gene is a very important piece of the biological masterpiece that is the human body, but due to a simple deletion of the amino acid, phenylalanine 508. Phenylalanine 508 is in one of the first nucleotide binding domains of the CFTR, so when being read all the subsequent nucleotides and amino acids are incorrect resulting in the cystic fibrosis disease. As unfortunate as it sounds, this genetic disorder is not entirely random. Inheriting one cystic fibrosis gene from each parent, like any other genetic based illness, is the main cause of the problem. Now, there is no reason to go banging on mom and dad's door looking for a fight, they did nothing wrong it is simply genetics at the end of the day. But there have been some relatively recent breakthroughs in forms of therapy to combat cystic fibrosis.

In the last twenty years, scientists have been able to find various treatments for the disease, mainly focused on prevention of the deletion within the phenylalanine 508 amino acid sequence. The Food and Drug Administration (FDA) has allowed for testing to be done within the CFTR on possible treatment pathways to find a cure of cystic fibrosis. The drug ivacaftor, a drug with the ability to treat cystic fibrosis through restoration of the chloride ion flow, has enabled a

genetic therapy for the disease. Unfortunately, this seemed much easier said than done since the typical gene therapy used for other genetic disorders has had much trouble arriving to the lungs, in some but not all of the patients this was tested on. With the small success of the ivacaftor, small molecule therapy has become the front runner in the race for the cure, though it has only helped of a minority of patients. With the addition of the lumacaftor, acting as a guide for protein folding within the CFTR, the numbers of patients with overall improvement have been vast, yet lumacaftor has had its own issues including, but not limited to, the destabilization of glycoform, a glycosylated variant, and low blood plasma levels, below thirty-four grams per liter. But the sky is the limit in the ongoing fight with cystic fibrosis since many of the large global pharmaceutical groups are continuing to do research on possible treatments and therapy based on their recent success in their labs.

Due to the many lethality of the genetic disorder of cystic fibrosis, affected patients begin to ask, why or how did this happen? With the help of genetics, scientists and researchers were able to provide an answer, a deletion within the cystic fibrosis transmembrane regulator gene (CFTR). One of the most lethal genetic disorders is solely created by a small deletion of a single amino acid sequence. As scary as that is, humanity has come together once again to find a cure, gene therapy is once again being utilized to restore the function and reverse the effects of cystic fibrosis, so once again the patients may live in peace. Although this appears to be an easy task, it is quite demanding. With more than a few years in the future of work to be done, treatment for the disease can be supplemented with gene therapy, using the drugs ivacaftor and lumacaftor for the almost ninety thousand patients with cystic fibrosis worldwide. Hope is in their hearts and on the horizon to delete this terrible deletion, and soon that goal will be accomplished.

Resources

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