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# Lethal Point Mutation Corrected In Vivo

Hutchinson-Gilford Progeria is a genetic condition usually caused by a random, single gene mutation. Under normal conditions, lamina A is the gene that codes for a protein used to ensure the stability of the nucleus of a cell. When this gene is mutated, the protein progerin is synthesized instead which makes the nucleus of a cell unstable. People who possess this point mutation will appear to age rapidly. Within their short lifespan of about fourteen years, they will experience premature hearing loss, hair loss, joint stiffness, atherosclerosis, osteoarthritis, and numerous other complications of this syndrome. Recently, a study was performed to see if this mutation could be corrected to prevent the creation of the pathogenic protein progerin and increase the stability of the nucleus to dampen the symptoms of this devastating syndrome.

This study used base editing to alter the mutated point mutation to the nonpathogenic form. More specifically, adenine base editing, ABE, was used in the lamina A gene to replace the adenine with the correct nucleotide, either cytosine or guanine. This editing was deemed successful because the pathogenic phenotype was decreased. To measure the effects of the edit, cells were harvested and analyzed from the test subject. In these cells, the pathogenic allele was corrected which reduced the amount of the pathogenic protein, progerin, in the cell which directly reduced the nuclear abnormalities that stem from this protein. Base editing was the chosen method in this study because it allowed the target allele to be altered while decreasing the number of unwanted derivatives. The ABE was used in fibroblasts from children and mice with Hutchinson-Gilford Progeria Syndrome. There was an 87-97% success rate of correcting the allele in the fibroblasts of children with the mutation.

While the adenine base editing, ABE, altered the desired gene, there was the possibility it was also editing other alleles that coded for nonpathogenic proteins. The DNA from the fibroblasts were analyzed by an unbiased party to detect any unfavorable results. It is important that this was done by an unbiased party to ensure that the results are accurate and are not skewed based on favorability. The third party did not detect any base editing in unwanted areas in the DNA of the fibroblasts.

An injection of a virus was created with the ABE to correct the pathogenic mutations. The virus, called adeno-associated virus 9 (AAV9), was injected into the retro-orbital sinus, behind the eye, of the mice with the mutation. Several mice were reported to have a notable correction of the pathogenic mutation. The mice were observed thoroughly to test for any changes. Six months after the injection was administered, 20-60% of the mice had a remarkable change in multiple organ systems from pathogenic mutation. The injection was then experimented in vivo. Finally, the AAV9 injection proved to improve the average lifespan by

almost double the lifespan with the pathogenic mutation by tackling the root of the cause of the syndrome, the DNA.

Work Cited

Koblan, L.W., et al. In Vivo Base Editing Rescues Hutchinson-Gilford Progeria Syndrome In Mice. *Nature* **589**. 608-614 (2021). https://www.nature.com/articles/s41586-020-03086-7.