CRISPR-Cas9 Treatment for People with Genetic Disorders

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Abstract:

CRISPR/Cas 9 is a new gene editing technology that can make precise changes in DNA. The CRISPR method is based on a natural system used by bacteria to protect themselves from viruses. It has shown great potential in treating genetic disorders: Down syndrome, by targeting extra copies of chromosome 21; sickle cell disease, by correcting mutations in the beta-globin gene to restore fetal hemoglobin; and CPS1 (Carbamoyl Phosphate Synthetase 1) deficiency, by fixing mutations that cause toxic accumulation of ammonia in the body. While CRISPR is a promising tool, the technology is still considered relatively new and can be further developed. This review aims to analyze the potential applications of CRISPR from the cellular level to real-life medical treatment, as well as the concerns of its usage. The paper also discusses each application of CRISPR in a range of genetic disorders. Understanding these aspects is crucial for future research and ensuring responsible implementations of CRISPR in medicine. One recent CRISPR advancement, including the first FDA-approved CRISPR-based therapy(Casgevy) and eventually, there will be further development using CRISPR.

Mechanism of the CRISPR-Cas9 system

What if we could improve genetic diseases with just a single cut of DNA? CRISPR is introducing new possibilities and ideas for scientists thinking about how to treat genetic conditions. CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats, and it was first discovered in 1987 by a researcher Ishino and his team(1). However, scientists did not fully understand this technique until the late 2000s when they realized CRISPR was a part of the bacterial immune system(1). CRISPR works by utilizing two components: repetitive DNA sequences, which are also known as CRISPR and Cas proteins. Cas proteins work like scissors that can cut DNA sequences. When a virus attacks a bacterium, a piece of the viral DNA is saved and later inserted into the CRISPR region of the bacterial genome. This allows the bacteria to “remember” the virus. If the same virus attacks again, the bacteria use this stored sequence to guide the Cas proteins to recognize and cut the viral DNA, stopping the infection. Scientists now use this technique as a tool to edit genes by guiding Cas proteins to specific parts of DNA in other organisms. Despite being a new gene editing technique, researchers have already started utilizing it in lab settings to fix damaging DNA mutations, and some positive results have been observed(14). One of the most promising uses of CRISPR is in treating genetic disorders caused by mutations or changes in a person’s DNA(14). Genetic disorders happen when there is a mutation or a change in the DNA sequence. A mutation can affect how cells grow and develop. Some people inherit these mutations from their parents, while others develop during the early stage of the cell cycle. CRISPR is one of many gene editing tools and it allows scientists to make changes in the DNA sequences in any cell or organism. What makes CRISPR unique is its precision and simplicity compared to other technologies. CRISPR utilizes a guide RNA to direct the Cas9 enzyme to a specific DNA sequence, allowing it to perform its

intended function. Because it is easier, faster to program, CRISPR has become a rising gene editing technology.

The CRISPR system is part of prokaryotic adaptive immunity, which is the immunity that an organism receives after exposure to an antigen(5). Scientists also discovered the CRISPR defense system. The system is divided into three stages: adaptation (acquisition of viral DNA), expression (making RNA copies of it), and interference (cutting down the matching virus DNA if it returns . First, the Cas9 protein can unwind DNA and has two domains with nuclease activity, allowing it to cleave the DNA double strand(3). CRISPR-Cas9 uses two main components: a specifically designed piece of RNA that matches the target DNA (sgRNA), and the Cas9 enzyme, which cuts the DNA at that exact location(3). Cas9 has the ability to target a specific DNA sequence due to the sgRNA guides Cas9 to its complementary DNA sequence through base pairing, and target recognition occurs only when a correct PAM sequence is present near the target site(21). Once the DNA is cut, the cell tries to repair it. Next, the guide RNA (gRNA), which is a combination of CRISPR RNA, which carries the sequence complementary to the target DNA and tracrRNA, which helps recruit and stabilize the Cas9 enzyme, enables the CRISPR Complex to search for the sequence of interest until the gRNA hybridizes with the DNA(14). The gRNA is a short synthetic RNA molecule used in the CRISPR-Cas9 system to guide the Cas9 protein to a specific DNA sequence. When there is a PAM region on the lower region of the DNA sequence, the nuclease domain becomes active and creates a cut that causes the double strand to break, which is then repaired in an error-prone manner. During this process, scientists can turn off a gene, fix a mutation, or insert new genetic material into the DNA sequence. This is possible because the cells repair breaks in two main ways: non-homologous end joining (NHEJ) and homology-directed repair (HDR)(21). In NHEJ, the cell quickly reconnects the broken DNA sequence, but often introduces small errors such as insertions or deletions that can disrupt the gene and effectively turn it off. While HDR is a more precise repair process that occurs when a piece of DNA is provided as a template. The cell uses this template to repair the break and allowing scientists to correct mutations or insert new genetic material. CRISPR systems are divided into two classes: Class I, which involves several proteins working together, and Class II, like CRISPR-Cas9, which only needs one protein to make the cut(3).

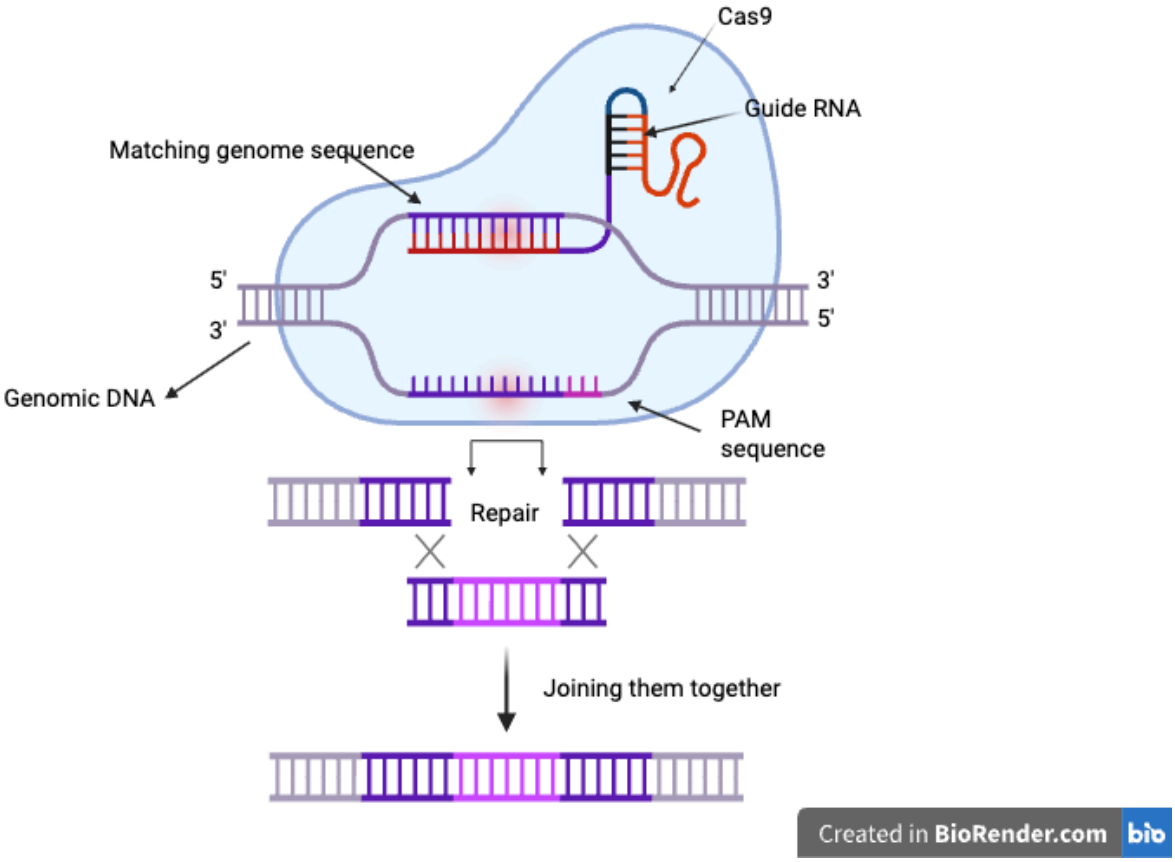

Figure 1: This image shows how the CRISPR-Cas9 system cuts DNA. (Figure created with BioRender)

The Cas9 protein is guided by a single-guide RNA (sgRNA) to a matching DNA sequence. The sgRNA is a short piece of RNA that has a 20-base sequence that matches the DNA sequences that need to be edited. Once it finds the target and a nearby PAM sequence, Cas9 creates a double-strand break at that location. A PAM sequence is a short DNA sequence that follows the DNA region targeted for cleavage by the CRISPR system, such as CRISPR-Cas9. Without the PAM sequence, Cas9 will not work(20). This allows scientists to edit the DNA during the cell's repair process. Although the technology is still in development, it's already showing positive results. It could potentially change the way we treat genetic diseases in the future, which would benefit many people with rare genetic disorders. Even though CRISPR is gaining more attention from scientists and developers, it's still a new technology to be used in real medical treatment.

Using CRISPR to Treat Down Syndrome

Scientists used CRISPR to remove extra chromosomes that cause Down syndrome and restore cell function. This is also the first time scientists have tried to fix the actual cause of a genetic disorder instead of just treating the symptoms(11).

Down syndrome is caused by an extra copy of chromosome 21 (Figure 2), which is also known as trisomy. The cause of this extra chromosome is usually a result of an error in the cell division

cycle during the early development of a fetus. This can affect how their brain and body work. There are three different causes of Down syndrome: trisomy 21, translocation and mosaicism. In fact, trisomy 21 makes up 95% of all cases of Down syndrome People with Down syndrome may look and act similarly but they all have different abilities. Down syndrome affects about 1 in every 1000 live births worldwide and it's also the most common chromosomal condition. To this day, there is no cure for Down Syndrome but there are many ways to provide a better quality of life for those with this disorder. Symptoms of Down Syndrome include a flat nose, short neck, narrow slanted eyes, small ears, hands and feet. As a person with this genetic disorder grows, other symptoms can arise, including vision problems, hearing loss and possibly congenital heart disease. According to statistics, people with Down syndrome are at a higher risk of developing Alzheimer's disease because of the presence of an extra chromosome 21.(9)

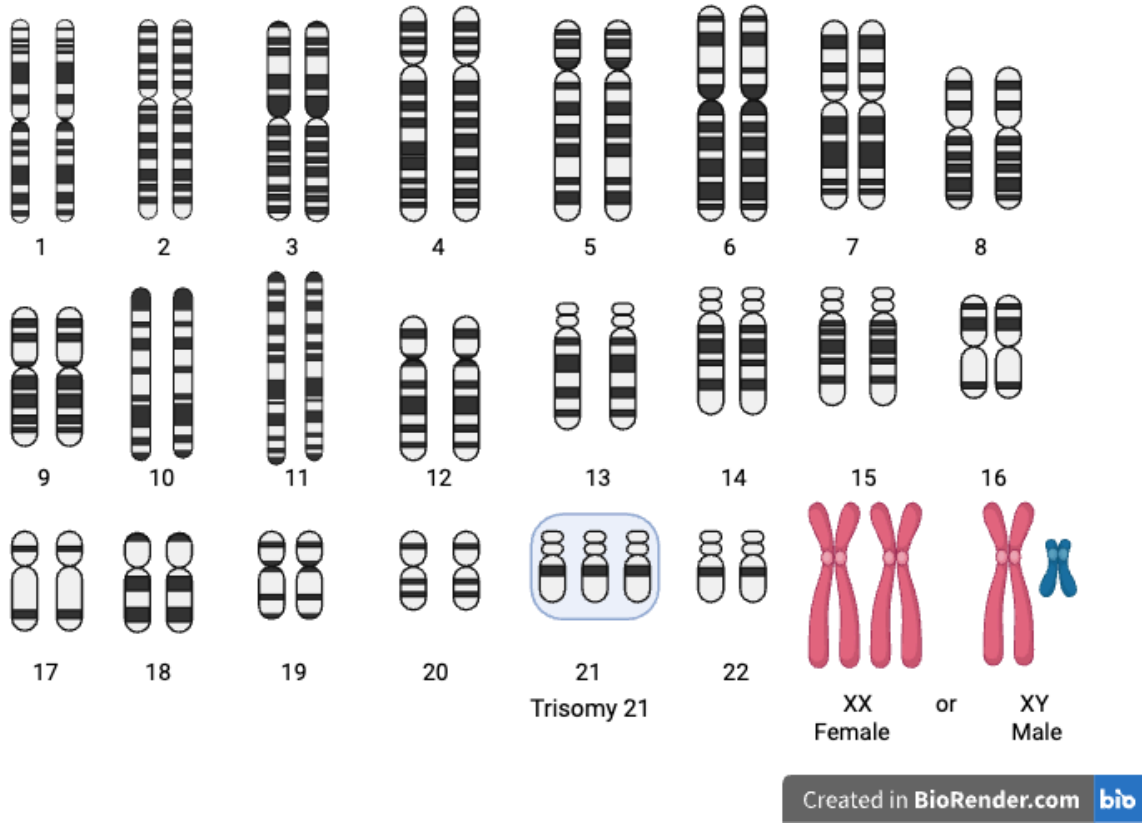

Figure 2: This image shows a human karyotype showing three copies of human chromosome 21 (Down Syndrome).(Figure created with BioRender)

As scientists search for ways to treat genetic disorders, CRISPR has shown much potential for this. Japanese scientists at Mie University have used the technique called "allele-specific editing"(AS), also known as CRISPR-Cas9 and they were able to target and remove only the extra copy of chromosome 21 while leaving the normal pair undamaged with a success rate up to 37.5%(16). Scientists were able to remove the duplicate chromosomes from both induced pluripotent stem cells and fibroblasts(16). The experiment shows that suppressing chromosomal DNA repair ability increased the rate of duplicate chromosome elimination. The CRISPR-Cas9

system has become a gene editing tool that helps scientists to insert, delete or change short DNA sequences at targeted locations in the genome. The developments of this technique have paved the way for future therapeutic interventions targeting aneuploidy syndromes, such as trisomy, that address the root cause of Down syndrome. Even though this study is performed in human cells and not living human, it has shown great potential for future treatment(12).

The researchers have developed an allele-specific (AS) Cas9 recognition sequence extraction method to target the extra copy of chromosome 21 in human trisomy 21 cells. This technique surprisingly can identify which chromosome has been duplicated which is necessary to ensure the cell does not end up having two identical copies after the removal but instead has one from each parent. They have found that the chromosome from both induced pluripotent cells and fibroblast cells suppresses the chromosomal DNA repair system by producing genes or proteins that interfere with normal repair processes. The discovery significantly increased the rate of duplicate chromosomes elimination. However, this method can not be used in real life yet due to the high risk of failure. Scientists suggested that this technique can eventually be used in brain cells and germ cells to compare the results between using different human cells(12).

CRISPR Applications in Sickle Cell Disease

CRISPR is also being used to treat genetic conditions such as sickle cell disease. Sickle cell disease is the most common form of an inherited blood disorder, affecting 70,000 to 100,000 Americans(2). People with sickle cell disease have abnormal hemoglobin, a type of red blood cell that carries oxygen in a disc shape(2). The disease causes the red blood cell to be rigid and sickle-shaped (Figure 3). This can block blood flow and prevent oxygen from reaching tissues and organs in the body, which can cause pain and inflammation(2). Right now, the major treatment for curing the disease is using hydroxyurea, which reduces sickling but it can cause some serious side effects(13). To be able to receive oxygen, fetuses must produce fetal hemoglobin, a form of hemoglobin that has a higher affinity for oxygen. This attracts oxygen and facilitates the movement of oxygen across the placenta, which allows the growing fetus to receive oxygen. The composition of fetal hemoglobin is also different from the adult hemoglobin. Sickle cell disease mainly affects the beta globin part of hemoglobin. Because newborn babies are born with mostly fetal hemoglobin, which contains gamma globin instead of beta globin, they usually do not show symptoms right away. Symptoms often begin to appear around four to six months of age, when the body starts switching from fetal hemoglobin to adult hemoglobin that includes beta globin.

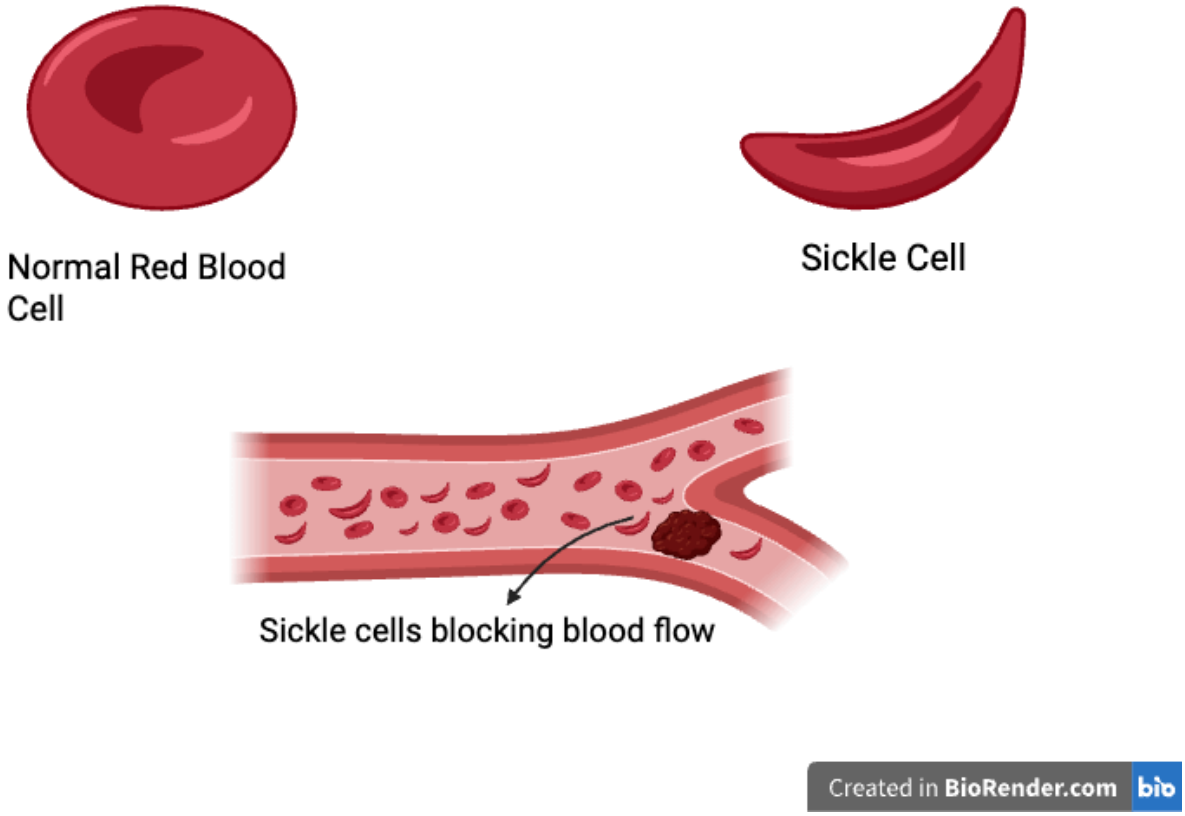

Figure 3: Showing sickle cells can cause blood clots and block blood flow. (Figure created with BioRender)

Scientists have been working and have recently developed CASGEVY(exagamglogene autotemcel) which is a gene therapy treatment for people over 12 years old with sickle cell disease or beta thalassemia(6). CASGEVY uses CRISPR editing technology and designs specifically for each patient using the patient's blood-forming stem cells(6). After birth, our human body tends to stop producing fetal hemoglobin. Around four to six months of age, the body starts switching from making gamma chains to making beta chains. This process is controlled by a protein called BCL11A(13), which turns off the gamma chain and turns on the beta chain. Scientists will insert the gRNA and Cas9 protein into the stem cells. The gRNA is designed to target a specific DNA sequence in the BCL11A gene enhancer. After that, Cas9 acts like molecular scissors, cutting the DNA at the BCL11A enhancer site and BCL11A can no longer suppress fetal hemoglobin production. When this switch happens, fetal hemoglobin increases and sickle hemoglobin decreases, which leads to the symptoms of sickle cell disease. CASGEVY works by pushing our body to keep producing fetal hemoglobin and for people with sickle cell disease, this also means that red blood cells keep their shape instead of turning into stiff, sickle-shaped cells, preventing pain and blood blockage. Treatment with CASGEVY starts approximately two months before stem cell collection(6). During this time, patients typically receive blood transfusions, which help to optimize the patient's conditions before the critical steps of the therapy. Scientists are treating sickle cell disease using an ex vivo procedure, which

means that the patient's stem cells are extracted, fixed the mutation and then replaced back into the body. On average, CASGEVY takes around 9 to 12 months to complete, and it is a custom treatment(6). This is also the first drug approved for direct CRISPR therapy. A medicine is given that mobilizes the stem cells are subsequently harvested using a process called apheresis and takes around 2 to 3 days to complete(6). Patients are usually hospitalized and under sedation, and then a catheter is placed into a vein. .The catheter is removed when the harvesting is completed. The stem cells are then transported to a specialized lab, where they are edited to produce CASGEVY(6). The production may take a few months and sometimes an extra round of harvesting needs to be done. After the cells are prepared, the patients are admitted to the hospital for four to six weeks. They are preconditioned with chemotherapy that wipes out the existing stem cells to make space for the treated ones. This sometimes leads to side effects such as low platelet and white blood cell counts. The treated cells are infused into the body about a week later through a single infusion. After infusion, the patients are kept under hospital care since the treated cells get implanted in the bone marrow and start producing new blood cells. Doctors are going to monitor for side effects such as low levels of platelet cells. Once the patients are discharged from the hospital, they still have to continue follow-up with regular check-ups for up to 15 years to evaluate the product safety and effectiveness. The United States Food and Drug Administration (FDA) also approved this treatment as the first medication to use CRISPR gene editing technology. In December 2023, it was approved for patients 12 years and older with sickle cell disease who experience frequent pain crises(6).

CRISPR in Treating Rare Metabolic Disorders: The Case of CPS1 Deficiency

There are two ways to treat diseases by modifying a patient's genes: In Vivo and Ex Vivo(18). Ex Vivo treatment is performed by removing a patient's cells and their DNA is edited outside the body, while In Vivo therapy is performed inside the body by injecting gene editing components. In vivo gene therapy is much simpler compared to Ex Vivo therapy. In vivo treatment occurs within the living organism, where many biological systems interact and influence the outcome(23). On the other hand, ex vivo using the isolated tissues removed from the organism, which simplifies the process and provides a more controlled environment(23).

One remarkable example of CRISPR being used in real life is the case of a baby boy born with a rare genetic disorder. A baby boy KJ, diagnosed with a rare metabolic disease known as severe carbamoyl phosphate synthetase 1 (CPS1) deficiency, which can also be known as a urea cycle disorder, has been treated with a customized CRISPR gene editing tool at the Children's Hospital of Philadelphia(7). CPS1 deficiency affects 1 in 1,300,000 persons and has an estimated mortality of 50% in early infancy(15).

Ahrens-Nicklas and Kiran Musunuru are both members of the NIH-funded Somatic Cell Genome Editing, have been collaborating to study the methods of creating gene editing therapy for individual patients since 2023(20). They are also spending years researching rare metabolic disorders that people have, as in the case of baby KJ(23). The doctors mainly focus on the urea cycle disorders and they found out that when our human body breaks down proteins, it usually produces ammonia which is then turned into urea in the liver and removed from the body through the urinary system(8). However, a child has urea cycle disorder is missing a major liver

enzyme and cannot perform this conversion. As a result, the level of ammonia in the body will increase and ultimately build up to toxic levels (hyperammonemia), damaging vital organs(8).

Scientists targeted KJ's CPS1 case for their study. KJ reported with severe high blood ammonia levels(>1000 μmol/L)(24). The baby's genetic testing revealed two mutations in the CSP1 gene: Q335X from the paternal allele and E714X from the maternal allele(24). At that time, the only way to treat his disease was a liver transplant, but with all the help from the hospital, the researchers were able to develop a personalized CRISPR-based editing therapy eliminating his Q335X mutation(24). Within just six months, their team has designed and made a base editing therapy delivered through lipid nanoparticles to fix KJ's faulty enzyme in his liver. In total, KJ has received three doses of the therapy on his restrictive diet(7). He received his first dose when he was 6 months old and got his two last doses after being carefully monitored. Luckily, no side effects have been reported. In this specific case, their team programmed CRISPR to go to the site of the genetic variant that causes the disease in the baby's body. Doctors could not get human liver cells with KJ mutations so they decided to use lab-grown liver cells(HuH-7) and mice with the same mutation(20). The treatment called k-abe was first tested on animals and showed promising results(20). The FDA has also approved this therapy and it was able for KJ to receive it(17). Because KJ is still a baby, the doctors only used a small amount of medicine to give to him for his body to adapt to it(7). The medicine acts as a drug delivered by an infusion and goes into his bloodstream until it reaches his liver. After a few days of getting his first shot, his body has already shown positive results(17). For example, he could tolerate more proteins without an increase in ammonia level like usual. Even though the treatment was not a full cure in this case due to CPS1 affecting a crucial metabolic pathway, and even a small amount of faulty cell activity can cause the symptoms again. But it has improved baby KJ's health significantly and he became the world's first patient treated with personalized CRISPR. On the other hand, getting a personalized gene editing treatment could be very expensive. This is because the process of creating this type of therapy is a complex process that requires significant time to develop, and implementing it effectively in the human body is challenging.

Ethical Concerns of CRISPR Gene Editing

While CRISPR gene editing is still a new technology, it has raised many ethical issues in the science world. One major concern is whether this technology is safe to use or not(12). Gene editing itself is not bad or good but it also depends on the applications. CRISPR can be used to control what genes get expressed or cut specific mutations in organisms(22). Like many advanced technologies, CRISPR is now being used in wealthy countries and it can cost approximately 2 million dollars per patient to get a genomic medicine(12). Due to the high cost, right now only the wealthy can possibly have access to them. People are also concerned that CRISPR has the potential to worsen the inequalities between the rich and the poor. Scientists are using CRISPR to treat somatic cells(12). Somatic cells are the ones that don't pass genetic traits to your children. But in the future, scientists might develop CRISPR to treat germline cells, which are also known as sperm cells and egg cells. This would mean that if we made any changes in the cells, we could pass them down to the next generation. In this way, we can protect our children from genetic disorders or common health issues. However, like many technologies, CRISPR can make mistakes. A recent study shows that a group of scientists tried

to use CRISPR to treat hereditary blindness and instead of correcting the genes, many of the embryos ended up losing chromosomes(22). Some cells even lost a large section of their genetic material, and unfortunately, in many cases, entire chromosomes were lost. Losing an entire chromosome is a big problem; for example, it can cause the deletion of specific genetic regions or errors during cell division. Most chromosomes have many essential genes, and having only one copy instead of two isn't enough for the embryo to grow properly. Losing a whole chromosome usually causes the embryo to stop developing and die because important genes are missing. Imagine this happened in embryos and later grew into babies, the consequences could be devastating. Many experts said that we do not fully understand the risks of using CRISPR, for example, unexpected genomic mutation and mosaicism can happen(10). Even though CRISPR has shown some successful results, using it on embryos is not guaranteed(22).

Currently, scientists use this technique mainly for medical purposes, but in the future, CRISPR may be used to edit traits that don't matter at all, such as eye color, height and so on. There are many cases where we were able to change the fur color of rats, which raises the question of whether this can also happen in the human body in the future(4). In 2015, a summit about human gene editing summarized that these experiments should only continue under strict and legal rules(18). Many countries, like the UK, the government only allow limited research on embryos, while others have completely banned gene editing. Genetically modified organisms (GMOs) designed with CRISPR can be an innovation in science but they can also change our ecosystem if released(4). One example is a modification of mosquitoes to prevent malaria that can affect other animals that we don't know. Because of all of these problems, it is very important that scientists manage and plan how to apply the CRISPR technique in the future.

Conclusion

CRISPR is a powerful tool that has already shown great potential to treat genetic disorders such as Down Syndrome, Sickle cell disease and even rare metabolic disorders. However, this technology is still new and could be developed further. If possible, CRISPR could also be used for non-medical purposes, such as agriculture purposes. Before CRISPR, gene editing was slow, expensive and messy but now, it is fast and accessible to many people. This does not mean that everyone can use CRISPR. Instead, researchers and scientists should have guidelines and regulations to ensure that CRISPR is used responsibly and only for medical purposes. As more research is being done with gene editing technologies, CRISPR offers hope for treating genetic disorders and improving human health.

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