Narrative Review Article

Treating Chromosomal Abnormalities with CRISPR Gene Editing

Eric Japson

Emerald High School, 3600 Central Parkway, Dublin, CA, 94568, United States

ABSTRACT

Chromosomal abnormalities, some of the most prevalent genetic diseases in the world, are caused when chromosomes are present in the wrong number or configuration. Some common types include duplications (more chromosomes than normal), deletions (less chromosomes than normal), and other structural issues (deletions, duplications, or inversions within one chromosome). Unfortunately, there are few available treatments for any of these diseases today. However, there have been several studies based on the possibility of using clustered regularly interspaced short palindromic repeats (CRISPR) proteins along with CRISPR-associated (Cas) proteins to treat these conditions. These methods range from using traditional CRISPR-Cas9 for treating duplications, utilizing integrase proteins to treat deletions, and employing gold nanoparticles to deliver CRISPR directly into the brain. CRISPR gene editing methods have the potential to become a widespread curative technique for chromosomal abnormalities. This review examines recent CRISPR advances to treat chromosomal abnormalities, including deletions, duplications, and structural aberrations.

Keywords: Genetics; CRISPR, Chromosomes; Chromosomal abnormalities; Aneuploidy

INTRODUCTION

Chromosomal abnormalities are some of the most common and debilitating diseases in the modern world. These include aneuploidy (having the incorrect number of chromosomes in the cell) or chromosomal damage such as deletions, duplications, and inversions. Common symptoms of these diseases include mental disability, short stature, and other physical defects. One other treatment currently in development is chromosome transfer, which involves lab-growing a copy of the missing chromosome and then implanting it into the cell (1). Unfortunately, this has the potential to lead to trisomy, as there is no guarantee that the offending copy of the chromosome will be removed (1). In addition, symptomatic relief drugs are widely available mechanisms for combating these diseases. However, these drugs only provide temporary relief for patients without actually treating the underlying disease. For instance, if a patient has Down syndrome, no drug they take will cure them of that condition, even if it does alleviate their symptoms.

However, CRISPR/Cas9 gene editing is a potential candidate for safe and efficient treatment of these conditions. Clustered regularly interspaced short palindromic repeats (CRISPR) is a bacterial defense mechanism against bacteriophages that involves the cutting of viral DNA by different types of Cas proteins, and more importantly, the copying of the viral DNA into the bacteria's genome (2). These features can be leveraged to edit the genome of human cells. The CRISPR-associated (Cas) protein (often Cas9) makes

Corresponding author: Eric Japson, E-mail: eric.daniel.japson@gmail.com.

Accepted December 23, 2025
https://doi.org/10.70251/HYJR2348.415966

cuts in the sections of DNA indicated by the guide RNA, which leads to the two main applications of CRISPR. Firstly, this cut, also known as a double-strand break (DSB), can be used to alter the genome if a template sequence is provided to use in place of the old one (Figure 1). The cell uses this sequence to patch the hole in its DNA, which can lead to the alteration of the targeted gene. On the other hand, if the cell is not provided with a template sequence, the cell repairs the DSB on its own using a process called non-homologous end joining (NHEJ). However, this often results in the "knock-out", or deactivation, of a gene as NHEJ is error-prone and will often introduce mutations into the genetic sequence (Figure 1).

A currently available CRISPR treatment is for sickle cell anemia (caused by a 1-base substitution in the beta-globin gene) and beta-thalassemia (3). The following sections will cover the different types of chromosomal abnormalities (duplications, deletions, and structural aberrations) and provide examples of how CRISPR is being tested to treat these abnormalities.

TREATING DUPLICATIONS

One common type of chromosomal abnormality that CRISPR could possibly treat in the future is chromosome duplication. This leads to aneuploidy, when there are the incorrect number of chromosomes in a cell. Specifically, many duplications lead to trisomy, where there are three copies of a chromosome instead of the normal two. These duplications typically form when gametes are performing meiosis. If the chromosomes do not separate correctly in Anaphase II, there will be a cell with three rather than two chromosomes and a cell with one chromosome instead of two. The most common chromosomes to be duplicated are 15, 16, 17, and 21. Some of the diseases caused by these duplications are Down syndrome (Trisomy 21), Patau syndrome (Trisomy 13), and Edwards syndrome (Trisomy 18) (Figure 2).

Down syndrome is one of the oldest recorded chromosomal abnormalities. It causes mental disability, short stature, and heart defects (3). While it does not directly decrease life expectancy, the quality of life can

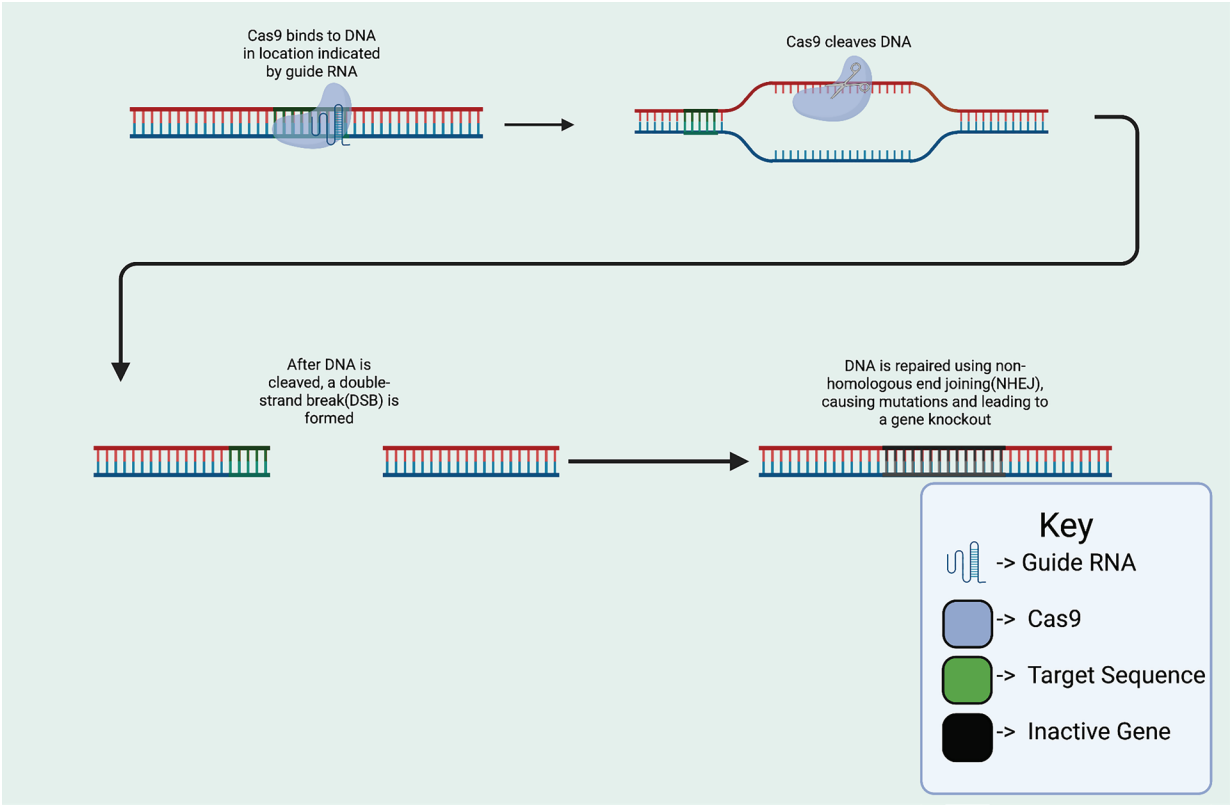

Figure 1. ***CRISPR Overview.*** *This figure depicts the process of knocking out a gene with Cas9, starting with a section of DNA and ending with a knocked out gene.Created using BioRender.*

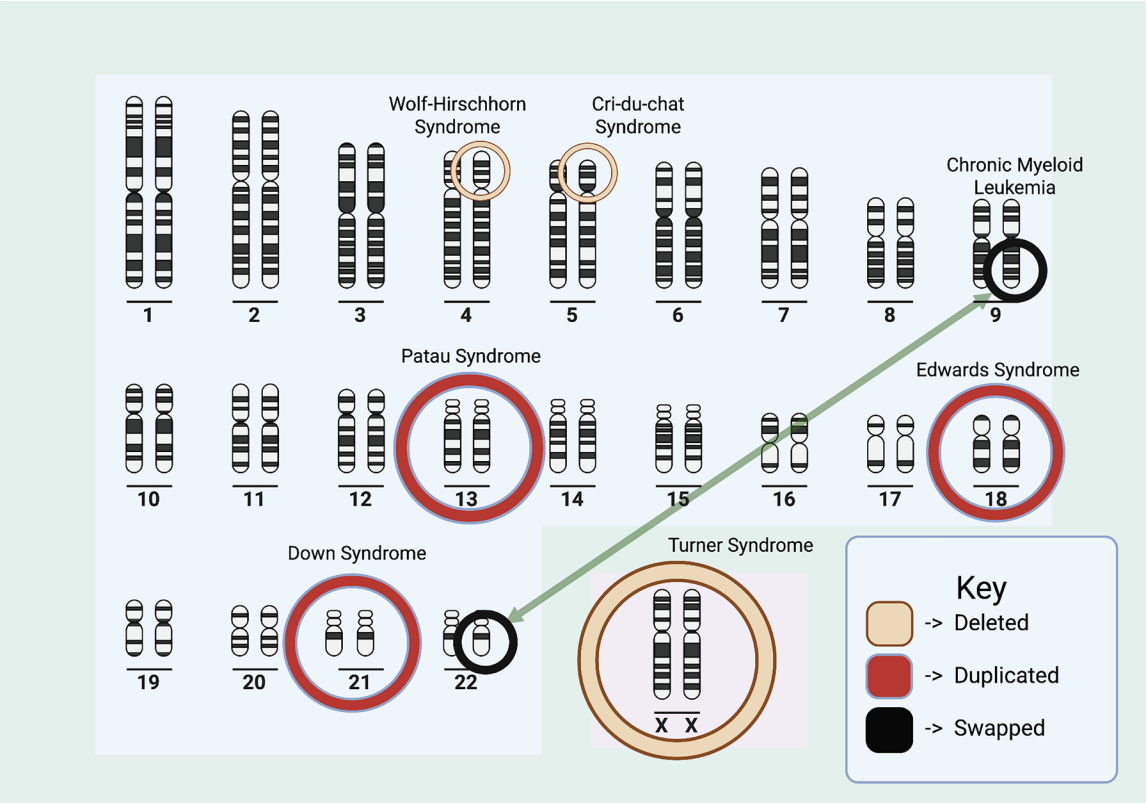

Figure 2. Normal Human Karyotype and Diseases. *The normal karyotype is shown. Deletions, duplications, and translocations are noted with colored circles. For deletions, large circles represent complete deletions and small circles represent partial deletions. The green arrow depicts the pieces of chromosomes that are swapped in chronic myeloid leukemia (CML). Created using BioRender.*

be drastically reduced. Common treatments today are symptom relief methods including surgery and special education (3).

Another disease caused by chromosomal abnormality is Patau syndrome. It is often immediately fatal after birth, with the average lifespan being just a few days and only 5-10% of babies reaching one year of age (4). It leads to malformed eyes, weak hearts, cleft lips, and poor muscle tone (4). Again, the only treatment is surgery for cleft lips and heart issues (4).

Finally, Edwards syndrome is another chromosomal abnormality that is immediately fatal and has no cure (5). Edwards syndrome causes slow prenatal growth, mental and physical disability, and clenched hands (5).

To sum up the current methods of treatments for chromosomal disorders, the only solution that we are turning to is to relieve the symptoms of the patient. However, this does not treat the underlying disease. CRISPR/Cas is currently emerging as a possible candidate for deleting an extra copy of the offending chromosome and curing the duplication. The basic idea of this method is to fragment the chromosome and cause it to truncate or break apart.

The first method uses Cas9 proteins to target the centromere of the chromosome. By finding repeating fragments at the centromere, the Cas9 can be used to cut the DNA at multiple points in that area (6). In a 2017 study by Adikusuma *et al*., two different gRNAs were found to make 140 and 41 cuts in the centromere area of the Y chromosome in mice embryos (7). These methods, called Centro 140X and Centro 41X respectively, led to successful deletions of the Y chromosome, up to 90% using Centro 41X (7). In addition to these methods, another gRNA known as Centro 2X was designed to flank the centromere on either side. This gRNA resulted in a 40% deletion of the Y chromosome (7). These methods could potentially be used in human embryos to target extra chromosomes as well (Figure 3).

A different approach entirely would include the use of a Cas3 protein in the place of a Cas9 one (8). The

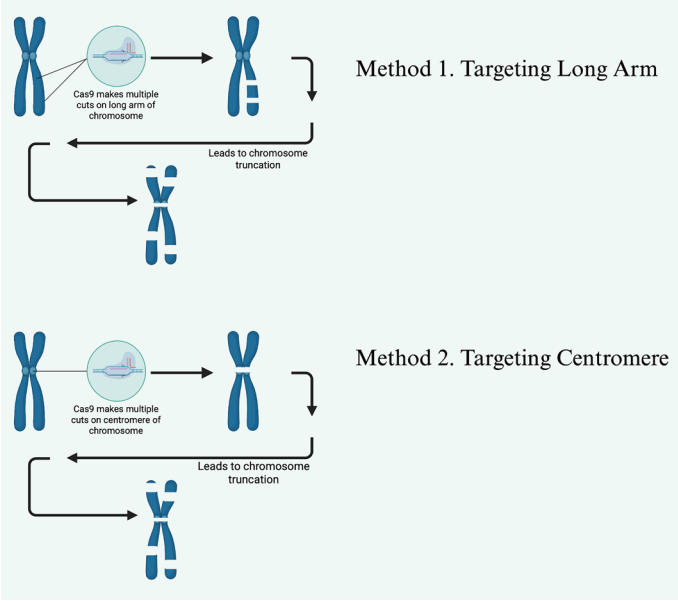

Figure 3. Deleting Chromosomes by Using Cas9 at Different Locations. *Both of the strategies listed above begin with a copy of the extra chromosome that needs to be deleted. After this, the Cas9 protein attaches to and makes cuts at either the centromere or the long arm of the chromosome. This then leads to the chromosome truncating, or breaking apart. Created using BioRender.*

Cas3 protein relies on a CRISPR-associated complex for antiviral defense (CASCADE) complex to guide it to the correct area, rather than a guide RNA. The CASCADE complex is made up of multiple proteins that allow it to bind and interact with the target DNA area, including Cas5, Cas6, Cas7, and Cse1 (8). Cas5 is responsible for binding to the guide RNA and forming the backbone of the whole CASCADE complex. The Cas6 is used for cleaving the crRNA into smaller pieces. The Cas7 makes up the backbone of the complex, protecting the crRNA. The Cse1 recognizes the protospacer-adjacent-motif (PAM) on the DNA sequence and facilitates the formation of the R-loop, a vital component of Cas3 (7). Once the whole complex is bonded to the DNA, instead of making a double-strand break like the Cas9, the Cas3 unwinds the helix of the DNA and moves along it, shredding it as it goes (8). This approach has been used to delete Y chromosomes in mice embryos while still retaining the *Sry* gene, a vital gene for gender differentiation that is located on the Y chromosome (9). Specifically, when sgRNAs were designed to target the 3' end of the DNA, 68.5% of the mice had fragmented Y chromosomes but intact Sry genes (9). This same method could be applied to human embryos and could potentially lead to the same chromosome deletions.

Cas3's ability to shred DNA makes it far more suited to larger deletions than Cas9, which can only make singular cuts. However, these deletions can be large and unpredictable, so safety measures are absolutely necessary for safe usage of this specific Cas protein (8). A common mechanism is to implant Anti-CRISPR (ACR) proteins into the genome (10). These proteins interfere with the Cas3 mechanisms, leading to it being unable to pass beyond that section. The ACR proteins are taken from bacteriophages that use them to combat CRISPR defenses (Figure 4).

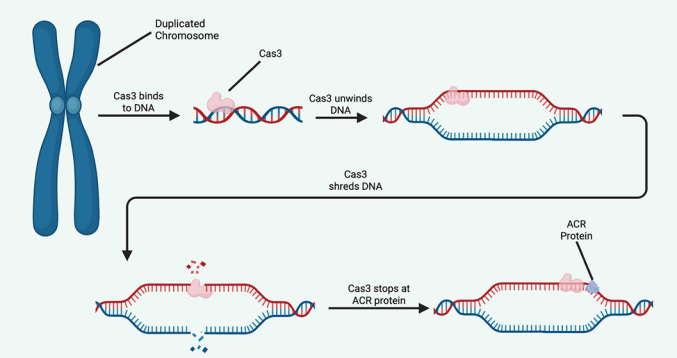

Figure 4. Using Cas3 to Delete Chromosomes. *In this figure, a Cas3 protein binds to the DNA on a duplicated chromosome and begins by unwinding the DNA. After this, the Cas3 moves along the DNA, shredding it as it goes. Once the Cas3 reaches the anti-CRISPR(ACR) protein, it is stopped from progressing any further, helping to reduce the risk of uncontrollable deletions. Created using BioRender.*

Cas9 and Cas3 both achieve the same purpose of destroying an extra chromosome, but the mechanisms that they use are very different. Cas9 uses many singular double-strand breaks at critical locations to break apart chromosomes, while Cas3 unwinds the DNA of the chromosome and shreds it apart. This makes Cas9 safer than Cas3 because of the decreased risk for uncontrolled deletions. However, Cas3 is also more efficient at deleting chromosomes due to the single cut site. However, there are still a few problems that need to be worked out regarding both of the methods. Namely, Cas3 CRISPR can still be very unpredictable and lead to catastrophic deletions in the cell. Secondly, Cas9 still suffers from off-target edits. Across both treatments, an important issue

is that the guide RNA will have to be custom-made for each and every patient.

TREATING DELETIONS

Another type of chromosomal abnormality targetable with CRISPR is deletions. Unfortunately, they are far more fatal than duplications. In fact, the only complete monosomy (only one copy of a chromosome due to a deletion) that is not fatal in utero is Turner syndrome, which involves the loss of one X chromosome. However, there are several other partial monosomies that include a partial loss of one of the chromosome arms.

Turner syndrome is characterized by the complete loss of an X chromosome. Patients will appear similar to people with an XX karyotype, but suffer from infertility, webbed neck, short stature, and swelling of the extremities (11). Additionally, 50-60% of patients with Turner syndrome have congenital heart diseases, typically narrowing of the aorta or issues with the aortic valve (11). Common treatments today include hormonal therapy and surgery, but the condition cannot be cured (11).

One of the most common partial monosomies is Cri-du-chat syndrome. It is caused by a deletion in the p arm of chromosome 5 (12). It causes poor muscle tone, small head size, low birth weight, and speech disability (12). In French, Cri-du-chat means "cry like a cat", which resembles the cry of a baby with this condition. The only treatments today are physical and speech therapy (12).

Another condition caused by a partial deletion is Wolf-Hirschhorn syndrome, caused by a deletion in the p arm of chromosome 4 (13). It leads to delayed development, low birth weight, underdeveloped muscles, scoliosis, and kyphosis (forward curvature of the spine) (13). Current treatments include physical therapy for muscles and surgery to correct the spinal deformities (13).

Again, there are no cures for these diseases today, but CRISPR has the potential to be a potential remedial treatment. However, instead of the typical Cas9 double-strand breaks made in traditional CRISPR treatments, there are other methods for inserting DNA into the genome.

One of the methods, Programmable Addition via Site-specific Targeting Elements (PASTE), relies on viral integrase proteins instead of Cas double-strand breaks to deliver DNA (14). Integrase is a protein commonly found in viruses, and its purpose is to facilitate the insertion of the phage's DNA into the host's. However, the integrase needs a specific landing site, called an AttP (14). This method uses a different form of Cas9, called nickase, to do its job (14). This nickase will only create a break in one strand of the DNA, not both. Then, the AttP can be inserted using the "nick" in the DNA. Once the AttP has been inserted into the genome, the integrase can then be used to deliver the DNA payload.

This method is far more efficient than traditional CRISPR methods, with a payload of up to 36 kilobases (kb), allowing it to facilitate larger gene additions. This method has been tested on mouse liver cells to insert genes into those cells (14). These results could potentially be utilized in human cells as well.

Another approach is to use transposons, or jumping genes, to insert DNA where it needs to go. Transposons are genes that can "jump" and move across sections of the genome (15). They can lead to disease and cause damage to the genome, but here they are leveraged to form a method for quick and effective insertion of large sections of DNA into the genome. An enzyme called transposase finds the repeats at both ends of the transposon and cleaves them there, freeing it from the genome. Then, sticky ends are made at the genome insertion point by creating a staggered cut rather than a straight one. This allows more DNA to join at either end because it leaves overhanging DNA that can be paired with the transposon, meaning that the jumping gene has been effectively taken from one area and used to patch another one. This is also less risky than Cas9 because the break is at a non-vital place in the genome, and it also has a much higher DNA payload (15).

These methods are better suited for adding back lost genetic material than traditional Cas methods, because traditional Cas methods are more focused on deleting sections of DNA than adding them. The main difference between the transposon method and the PASTE method is that the PASTE method requires extra proteins to be utilized to insert DNA, while the transposon method uses genes already part of the genome to function. This could potentially impact the viability of PASTE for larger additions, because the extra proteins present another point of failure. On top of this, PASTE methods can sometimes run into DNA binding issues, where the integrase is unable to connect to the AttP landing pad. One limitation of the transposon method is that it can lead to off-target edits.

TREATING STRUCTURAL ABERRATIONS

The last type of chromosomal abnormality that CRISPR gene editing has the potential to treat is

structural aberrations, or chromosomal damage. These can include translocations and insertions. These abnormalities are typically not as visible on a karyotype as deletions or duplications, but they can still cause illness. A translocation is when a section of a chromosome breaks off and reattaches itself to a different chromosome, leading to gene fusion mutations. This can either be a reciprocal translocation (when the genetic material is swapped) or a Robertsonian translocation (where genetic material is added to one chromosome and taken away from another). An insertion is when a section of DNA is inserted into the chromosome, such as a nucleotide repeat.

An example of a disease caused by a translocation is chronic myeloid leukemia. It occurs when sections of chromosomes 9 and 22 swap, causing the BCR gene on chromosome 9 to fuse with the ABL1 gene on chromosome 22, forming the BCR-ABL1 gene (16). Both the BCR and ABL1 gene provide instructions for cell growth and development. However, the mutated BCR-ABL1 gene facilitates uncontrolled growth of white blood cells, which leads to leukemia (15). This gene can be knocked out using traditional CRISPR/Cas9 techniques, and it has been tested in mice (Figure 5).

As for insertions, an example of a condition would be Fragile X syndrome. The X chromosome has nucleotide repeats of CGG in the FMR1 gene, and abnormal repetition of this section can lead to disease (17). This condition causes mental disability and distinctive physical features such as sunken chest, large ears, and flat feet (18). The repeat on the X chromosome disrupts the function of the FMR1 gene, which is vital for brain synapses. The synapses are what carry the electrical signals throughout the brain and problems with these are what lead to mental disability (17). Cutting out this repeat would be an effective way of mitigating this disease.

Trials in mice have been conducted with a nonviral vector known as CRISPR-Gold (17). This nonviral vector gets around the issues of immune responses by using a gold nanoparticle with the CRISPR machinery attached to it. This complex is then injected into the brain of the mouse, which leads to the repeat being cut out by the CRISPR (18). This technique was used in Ai9 genetically modified mice with a fluorescent *TdTomato* gene followed by a stop signal (17). Thus, when the stop signal is deleted, the fluorescence is exhibited (17). Using

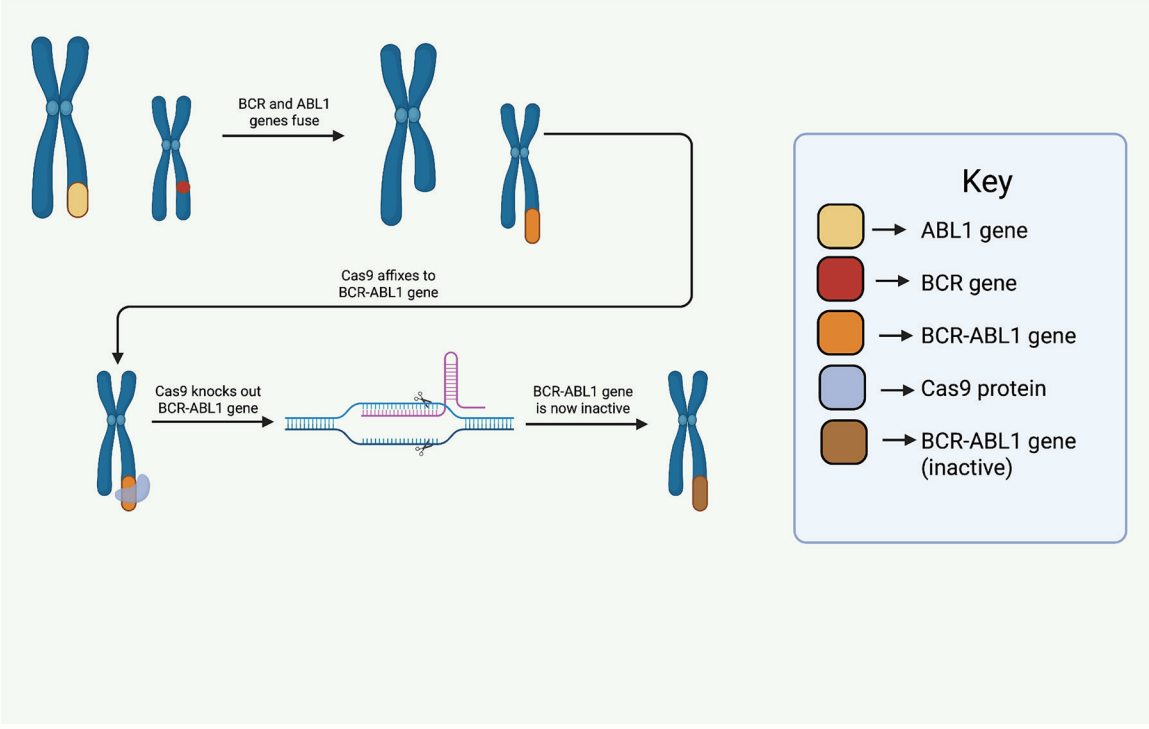

Figure 5. ***Using Cas9 to Treat Chronic Myeloid Leukemia.*** *CML is caused when sections of chromosomes 9 and 22 swap, fusing the BCR and ABL1 genes together. This results in the mutated BCR-ABL1 gene. To treat this condition, Cas9 is used to knock out the BCR-ABL1 gene and deactivate it. Created using BioRender.*

the CRISPR-Gold technique, 10-15% of stop signals were deleted and the *TdTomato* gene was expressed. This same mechanism has the potential to be used in human cells as well, to cut out repetitions that occur in Fragile X Syndrome.

These two methods have been some of the most advanced techniques tested to treat these chromosomal aberrations, and they have the potential to be utilized in the future.

CONCLUSION

CRISPR gene editing is a promising method for treating chromosomal abnormalities. There are many methods of doing so, including using Cas9, Cas3, and integrase proteins to treat duplications, deletions, and inversions. In addition, CRISPR is not just a tool for treating diseases. It can also be used to induce various abnormalities into cells for the purpose of studying them. There are several methods to cause insertions, deletions, duplications, and more in cells (19).

Despite all of its theoretical advantages, CRISPR gene editing still has its problems that need to be solved in order to produce a viable treatment option. First of all, all of these methods have only been tested in mouse embryos. These editing techniques would be far riskier in human embryos, and even more so in a living patient. There is always a risk of off-target edits with CRISPR, which can lead to catastrophic mutations. Making that error in a human would be costly. Moreover, the process itself is very tedious and labor-intensive. Every patient will need a unique gRNA for their treatment due to differences in their DNA. This could possibly drive-up costs, leading to an insurmountable barrier in access for some individuals. For example, the cost for CRISPR sickle cell treatment, the only commercially available sickle cell cure, can be as high as 2.2 million dollars per patient. This price can be a large burden on patients, hospital staff, and insurance companies (20). Another potential barrier for CRISPR viability is the complexity of getting the CRISPR/Cas complex into all of the cells of an entire human body. Because there are so many cells in the human body, there is no guarantee that the CRISPR complex will be able to make it into all of the cells. The methods of delivery to different types of tissues are different, meaning that there is no way to get the CRISPR into every cell of the body. As a result, it is not certain that treatment in a whole human will succeed. Before CRISPR gene editing can be used as a valid treatment for chromosomal disorders, these issues must be resolved.

There are some methods that can be used to mitigate some of the problems with CRISPR gene editing. For instance, editing a human embryo would be much easier than editing a whole human body because the number of cells is much lower. To accommodate this, prenatal genetic testing would be required to confirm if the embryo would actually have a condition. In addition, future clinical trials would be needed to confirm that the results on mice would be the same in humans. However, there are also complex ethics surrounding CRISPR gene editing. For example, it may not be ethical to use human embryos for testing. In addition, prenatal genetic testing also comes with many ethical problems. Specifically, it may lead to privacy issues, where one's genetic information could be sold to various companies.

In conclusion, CRISPR/Cas gene editing techniques are being tested to treat and cure chromosomal abnormalities, including duplications, deletions, and inversions. It does this by using different proteins, including Cas9, Cas3, integrase, and more. Though it is not without its challenges, CRISPR gene editing shows promise to be a curative technique for chromosomal abnormalities.

ACKNOWLEDGEMENTS

This project was completed under the guidance of a PhD student mentor, Sophie Karolczak.

FUNDING SOURCES

No funding was received for this project.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this work.

REFERENCES

1. Paulis M, *et al*. Chromosome transplantation: a possible approach to treat human X-linked disorders. *Molecular Therapy - Methods & Clinical Development*. 2020 Jan; 17: 369-77. https://doi.org/10.1016/j.omtm.2020.01.003
2. Yuanwu Ma, *et al*. Genome modification by crispr/cas9. *The FEBS Journal*. 2014; 281 (23): 5186-5193. https://doi.org/10.1111/febs.13110.
3. Park, *et al*. CRISPR/Cas9 gene editing for curing

sickle cell disease. *Transfusion and Apheresis Science [Internet]*. 2021 Jan 10; 60 (1): 103060. https://doi.org/10.1016/j.transci.2021.103060

4. Down Syndrome. Available from: https://medlineplus.gov/downsyndrome.html (Accessed 2025-08-24)
5. Patau Syndrome. Available from: https://medlineplus.gov/genetics/condition/trisomy-13/ (Accessed 2025-08-25)
6. Edwards Syndrome. Available from: https://medlineplus.gov/genetics/condition/trisomy-18/ (Accessed 20 25-08-27)
7. Adikusuma F, *et al*. Targeted Deletion of an Entire Chromosome Using CRISPR/Cas9. *Molecular Therapy*. 2017 Aug; 25 (8): 1736-8. https://doi.org/10.1016/j.ymthe.2017.05.021
8. He L, *et al*. Cas3 Protein-A Review of a Multi-Tasking Machine. *Genes [Internet]*. 2020 Feb 18; 11 (2). https://doi.org/10.3390/genes11020208
9. Li J, *et al*. Precise large-fragment deletions in mammalian cells and mice generated by dCas9-controlled CRISPR/Cas3. *Science Advances*. 2024 Mar; 15: 10 (11). https://doi.org/10.1126/sciadv.adk8052
10. Marino ND, *et al*. Anti-CRISPR protein applications: natural brakes for CRISPR-Cas technologies. *Nature Methods [Internet]*. 2020 Mar 16; 17 (5): 471-9. https://doi.org/10.1038/s41592-020-0771-6
11. Turner syndrome. Available from: https://medlineplus.gov/genetics/condition/turner-syndrome/ (Accessed 20 25-08-27)
12. Cri-du-chat Syndrome. Available from: https://medlineplus.gov/genetics/condition/cri-du-chat-syndrome/ (Accessed 2025-08-27)
13. Wolf-Hirschhorn Syndrome. Available from: https://medlineplus.gov/genetics/condition/wolf-hirschhorn-syndrome/ (Accessed 2025-08-28)
14. Yarnall MTN, *et al*. Drag-and-drop genome insertion of large sequences without double-strand DNA cleavage using CRISPR-directed integrases. *Nature Biotechnology*. 2022 Nov 24; 41 (4). https://doi.org/10.1038/s41587-022-01527-4
15. Lampe GD, *et al*. Structure-guided engineering of type I-F CASTs for targeted gene insertion in human cells. *bioRxiv (Cold Spring Harbor Laboratory)*. 2024 Sep 19; https://doi.org/10.1101/2024.09.19.613948
16. Vuelta E, *et al*. Future Approaches for Treating Chronic Myeloid Leukemia: CRISPR Therapy. *Biology [Internet]*. 2021 Feb 1; 10 (2): 118. https://doi.org/10.3390/biology10020118
17. Fragile X Syndrome. Available from: https://medlineplus.gov/genetics/condition/fragile-x-syndrome/ (Accessed 2025-08-29)
18. Lee B, *et al*. Nanoparticle delivery of CRISPR into the brain rescues a mouse model of fragile X syndrome from exaggerated repetitive behaviours. *Nature Biomedical Engineering*. 2018; 2 (7): 497-507. https://doi.org/10.1038/s41551-018-0252-8
19. Rueda J, *et al*. Affordable pricing of CRISPR treatments is a pressing ethical imperative. *The CRISPR Journal [Internet]*. 2024 Oct 10; 7 (5). https://doi.org/10.1089/crispr.2024.0042
20. Bosco N, *et al*. KaryoCreate: A CRISPR-based technology to study chromosome-specific aneuploidy by targeting human centromeres. *Cell [Internet]*. 2023; 186 (9): 1985-2001.e19. https://doi.org/10.1016/j.cell.2023.03.029