The Potential and Challenges of Gene Editing Technology in the Treatment of Rare Genetic Diseases

Ziming Wang *

Guangdong Overseas Chinese High School, Guangzhou, 510030, China

* Corresponding Author Email: wangziming071129@163.com

Abstract. Rare genetic disorders represent serious health challenges for patients with few treatment options available through traditional methods. New gene editing technology, specifically CRISPR-Cas9, has the ability to revolutionize the treatment of these disorders by providing options for precision therapy aimed at specific single gene mutations. This review examines the immense possibilities gene editing technology holds for the treatment of rare genetic disorders and the advantages of precision target discovery, one-time potential cure therapy, and individualized therapies. Documented successful case studies exist for CPS1 deficiency, beta-thalassemia and sickle cell disease. However, the technology is limited by many restraining factors as well, including off-target effects, delivery effectiveness, long-term safety and efficacy issues, ethical dilemmas, and regulatory problems that remain to be addressed. Future promises of gene editing technology to aid patients with rare diseases involve the continued development of more precise editing tools, advancement in delivery methodology, long-term evaluative studies on safety and efficacy of new technology, as well as ethical and regulatory environments designed to test and refresh the concepts of safety, efficacy and access to patients impacted by technology. Gene editing technology holds the promise of new hope for patients afflicted with rare diseases, but the advent of new technology must take into consideration the pluses and minuses of its potential use.

Keywords: gene editing technology; rare genetic disease; potential and challenges; CRISPR-Cas9.

1. Introduction

Rare genetic diseases typically refer to a category of conditions caused by gene mutations with extremely low prevalence rates. According to the World Health Organization (WHO) definition, rare diseases generally have an incidence rate below 1 in 2,000. Over 7,000 rare diseases have been identified globally, with approximately 80% having a genetic basis [1]. Although the number of patients with any single rare disease is small, the overall patient population is large. Since most rare genetic diseases have early onset, rapid progression, and high rates of disability and mortality, patients and their families bear a heavy physical, psychological, and financial burden.

The treatment options for rare genetic diseases have, for so long, been extremely limited. The traditional treatment options that do exist almost entirely consist of methods of symptomatic support, such as enzyme replacement therapy, drug mediated control of metabolic pathways, or organ transplantation. These will often only work to slow the progression of disease, never to cure the underlying defect, and they are also accompanied by a variety of shortcomings such as unreliable efficacy, cost and debilitating necessity for long-term treatment. For example, while patients who suffer from spinal muscular atrophy (SMA) may improve motor function through flexible use of nusinersen, this must be given thereafter through continual intrathecal injections and results in an extremely expensive form of treatment. Methods by which therapeutic means may be developed, that may cure the underlying defect at its source, represent an urgent necessity for the medical community to develop.

With the rapid development of molecular biology and genomics, gene therapy is gradually showing the potential to cure monogeneic genetic diseases. Especially in recent years, the breakthrough of gene editing technology has provided unprecedented tools for precise intervention of pathogenic genes. From early zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) to the birth of the CRISPR-Cas9 system in 2012, gene editing has achieved a transformation from "difficult to manipulate" to "highly efficient, programmable, low-cost" [2].

CRISPR technology can accurately target specific DNA sequences through guide RNA (gRNA), apply Cas nucleases for specific cleavage, and utilize the cell's own repair mechanisms, thus realizing gene editing, knockout or insertion. A "one-time cure" for genetic diseases is possible.

At present, multiple CRISPR-based clinical trials have made remarkable progress in the field of rare genetic diseases. For example, the CTX001 therapy has achieved clinical cure in patients with beta thalassemia and sickle cell disease; the in vivo CRISPR editing of hepatocytes for the treatment of transthyretin amyloidopathy (ATTR) has significantly reduced the content of the pathogenic protein of this disease [3]. All these advances represent the transition of gene editing technology from the laboratory to the clinical application stage, and will play a leading role in the development of gene editing technology and treatment of rare diseases. However, at present, gene editing technology, despite its very high clinical development potential, still faces a lot of difficulties, such as off-target effect in genetic modification, delivery efficiency of gene editing system, long-term safety of gene editing, and ethical problems. How to promote and develop scientific research technology and promote the scientific and technological progress of gene editing, at the same time, fully guaranteeing the safety, justice and ethical compliance of gene editing technology in application and practice, has become the focus of the attention of the scientific community of the world, ethics committees and regulators. This paper systematically discusses the therapeutic application of gene editing technology in rare genetic diseases, reviews and analyzes the current technical, ethical and regulatory problems, analyzes the difficulties, and describes the direction of future research and development. Provide theoretical guidance and practical help for scientific research and clinical transformation in this field.

2. Principle and main tools of gene editing technology

Gene editing technology is an accurate gene manipulation method that can modify the genome of an organism, thus changing its genetic characteristics [4]. The core principle of this technology is to use the mechanism of DNA double-strand break and repair to achieve accurate cutting, insertion or deletion of genes by introducing specific nucleic acid sequences. Table 1 below is a comparison of mainstream gene editing technologies.

Table 1. Comparison of mainstream gene editing technologies

Technical name	Principle	Advantage	Disadvantage
CRISPR-Cas9	Utilizes Cas9 nuclease and guide RNA (gRNA) to recognize and cleave specific DNA sequences [5].	Simple operation, low cost, accurate editing sites and a low off-target rate.	Potential for low editing efficiency and poor specificity.
ZFNs	Specific DNA sequences are recognized by zinc finger proteins and cut [6].	The first generation of gene editing technology; it relies on the function of realizing zinc finger proteins based on unique DNA sequence recognition.	The design is complicated and highly dependent on the target sequence and its upstream and downstream sequences, with high off-target rate and high cytotoxicity.
TALENs	TALEN elements are targeted and bound to specific DNA sites by DNA recognition module, and then the specific site is cut under the action of FokI nuclease [7].	Compared with ZFN technology, the design is simpler and more specific.	It is cytotoxic, and at the same time, the assembly process of the module is complicated, which requires a lot of sequencing work, and usually large companies are able to carry it out, and the cost is high.

The CRISPR-Cas9 system is currently the most widely used gene editing tool, originating from the innate immune mechanism of bacteria. This system consists of the Cas9 protein and a specific RNA sequence. The RNA sequence pairs complementarily with the target DNA sequence, guiding the Cas9 protein to locate specific genomic positions. The Cas9 protein possesses "nuclease" activity, capable of creating double-strand breaks at the target DNA sequence. Under the influence of the cell's own DNA repair mechanisms, the broken double-stranded DNA is repaired, thereby enabling the insertion, deletion, or replacement of specific gene segments [8].

Zinc finger nucleases (ZFNs) technology is the first generation of genome editing tools that are based upon the family of zinc finger proteins that exhibit unique DNA recognition. TALEN (transcription activator-like effector nucleases) technology functions by systematically introducing TALEN components that specifically bind to target genomic DNA sequences utilizing their DNA recognizing regions, while the FokI nuclease promotes cleavage at the selected genomic DNA target site. The TALEN tools utilize the endogenous cellular homology directed repair (HDR) or non-homologous end joining (NHEJ) repair pathways permitting the insertion (or inversion) of specific DNA sequences, deletion of specific DNA sequences, or fusion of specific DNA sequences [9].

3. Potential of gene editing in the treatment of rare genetic diseases

3.1. Technical superiority

Gene-editing techniques, especially the CRISPR/Cas9 system, operate through guide RNA (gRNA) that targets the precise loci of the pathogenic gene where expression of the gene is disturbed. These techniques utilize nucleases such as Cas9 to produce site specific DNA breakage and use the capacity of the cells to repair DNA to allow correction or replacement of defective genes. This allows specific identification of isolated single gene mutations and for effecting repair without interference in healthy genes. A single round of gene editing may produce a long-lasting or permanent therapeutic effect thus abolishing the necessity of repeated treatment. Theoretical applicability to almost all hereditary diseases due to single gene mutation gives it a universal approach for treatment of diseases of low prevalence. As compared with conventional drugs the gene editing treatments may be quickly modified to allow the means of delivering personalized precision medicines.

3.2. Typical treatment cases

A university team developed a customized gene editing drug K-ABE for a baby KJ with CPS1 deficiency (a rare disorder of urea circulation) in just six months. After treatment, the key indexes such as blood ammonia were significantly improved, and the nervous system was not further damaged, showing unprecedented potential for individualized and precise treatment [10]. Related teams published research detailing how they successfully cured 5 patients with β-thalassemia by using CRISPR-Cas9 technology. By accurately repairing the HBB gene mutation, the patient's hemoglobin level returned to more than 90% of the normal range within 12 weeks, and there was no off-target effect. It has been recognized by FDA for breakthrough therapy and is expected to be commercialized in 2025 [11]. Casgevy, the world's first CRISPR gene editing drug, has been approved for the treatment of sickle cell disease, marking the practical stage of gene editing therapy [12]. In vivo CRISPR therapy NTLA-2002 can reduce the average attack rate of patients by 95%, and some patients have no attack for one year, which shows the potential of functional cure [13]. The lead editing technology successfully repaired the pathogenic gene in the mouse model, significantly improved the neurological symptoms, and opened up a new path for the treatment of brain genetic diseases [14].

3.3. Frontier technological breakthrough

New editing tools developed by related teams can accurately embed complete genes or realize multi-base editing, greatly reducing the risk of off-target and improving the safety of treatment. Delivery technologies such as lipid nanoparticles (LNP) and AAV virus vectors are becoming more

and more mature, enabling gene editing tools to directly reach key tissues such as liver and brain [15]. Accurate repair of single base mutation by efficient base editor has achieved remarkable effect in rare diseases such as CPS1 [16].

With the maturity of CRISPR technology, gene editing therapy is accelerating to the clinic and the market. According to the industry forecast, the global CRISPR gene therapy market will grow at an average annual rate of more than 20% in the next five years, and the treatment of rare diseases will become an important growth point. Many enterprises at home and abroad have laid out gene editing pipelines, and some products have entered phase II clinical practice, and the commercialization path is gradually clear.

4. Challenges and risks faced

4.1. Technical challenges

Although tools such as CRISPR/Cas9 have greatly improved the editing accuracy, due to the complexity of gene sequence and individual differences, non-target genes may still be cut by mistake (off-target effect), resulting in unpredictable mutation or abnormal function. In the case of complex genomic regions or highly conserved sequences, it is more difficult to locate the target gene accurately. At present, the success rate of gene repair is limited, especially in polygenic genetic diseases. This may lead to an unstable treatment effect, and it may need many operations to achieve the expected effect. How to transport editing tools to specific cells efficiently and safely is still a difficult problem. Viral vectors may have immunogenicity risks, while non-viral methods face the problem of low transfection efficiency. In addition, environmental interference in the process of cell separation and in vitro culture may also affect the final curative effect. The long-term stability of cells or tissues after gene editing is not yet clear, and the potential risks include the accumulation of gene mutations leading to secondary tumors or other genetic diseases. In vivo experiments show that some patients may have inflammatory reaction or tissue damage. Exogenous editing components may trigger the body's immune system to attack its own cells, affecting the therapeutic effect and aggravating the disease. For example, antibody production against Cas9 protein will reduce the effectiveness of repeated administration.

4.2. Ethics and social challenges

The application of technology involving genetic changes breaks through the traditional ethical boundary, which may affect the health of future generations and the diversity of human gene pool, and lead to moral panic such as "designing babies". Supporters believe that it can be used to eliminate serious genetic defects, but opponents worry about slipping into the direction of non-therapeutic enhancement. The high cost of treatment makes this technology a privilege for the rich and aggravates the uneven distribution of medical resources. Only a few top medical institutions in the world have the implementation conditions, and most patients cannot benefit from it for economic reasons. Patients with rare diseases are often in a weak position and it is difficult to fully understand the technical risks. Language and cultural differences further weaken the authenticity and voluntariness of informed consent. Once the patient's genetic information is abused, it may lead to discrimination in employment, insurance and other fields. At the same time, poor database management may cause sensitive data leakage and threaten personal privacy. Different cultures' cognitive differences on the nature of life lead to uneven acceptance. Religious groups may regard gene intervention as a violation of natural laws, while the public is worried about the consequences of out-of-control technology.

4.3. Supervision and legal challenges

The existing framework is difficult to adapt to the rapid development of gene therapy, such as the lack of clinical trial design standards, vague product approval paths and other outstanding problems. Policy differences among countries further hinder international cooperation research. In case of adverse events, there is no clear basis for the division of responsibilities among medical institutions,

researchers and enterprises. Especially in transnational experiments, the application of conflict of laws makes the accountability more complicated. Core patents are concentrated in the hands of a few companies, which limits the space for technology popularization and price reduction. The lack of open access mechanism prevents small and medium-sized institutions from participating in innovation competition. Large-scale clinical trials produce massive genomic data, and how to promote scientific research cooperation while ensuring personal information security has become a key issue. Cross-border data transmission also involves sovereignty jurisdiction disputes. The attitudes of countries to gene editing range from strict prohibition to loose encouragement, and the lack of unified global governance rules may lead to "race to the bottom". Although WHO promotes the formulation of guidelines, its binding force is limited.

5. Future Prospects and Development Directions

Gene editing technologies, particularly the CRISPR-Cas9 system, are expected to continue evolving to become more effective and safer. In particular, the emergence of CRISPR-Cas12a and new gene editing technologies such as base editors and PrimeEditing, will allow more precise gene editing to be performed. Gene editing technology will develop the field of personalized medicine, through analysis of genetic data from patients and modifications being customized to the patients' own genes so as to achieve the best therapeutic outcome. Gene editing will find wider application in treating rare diseases such as cystic fibrosis, hemophilia and thalassemia as the technology matures. Increasing affordability and improvements in the degree of efficacy of gene editing therapies will lead to decreasing costs of gene editing therapies, with more patients being able to benefit.

Further studies are needed and certainty must be gained as to the safe and efficient results to be expected from the gene-editing process, in order to guarantee the definiteness of the assurances of the efficacy of the treatment in general while diminishing the dread possibilities that exist. The ethical problems that arise from its practice must be properly faced, such as the moral limitations of the uses of the gene-editing technology and the safeguarding of the privacy of the subject. But it is essential to promote awareness of this technology so that it can be made in the future beneficial to more patients. This can be very effective in increasing public knowledge and greater acceptance of the technology. The development of the processes by means of the gene-editing principle necessitates the collaboration of the many branches of knowledge such as biologists, medical professionals, ethicists, and law makers. Some codification must also be laid down with the development of gene editing, in order to point out the limitations set down for the legitimate application and management of the technology itself.

Gene editing technology has great potential in the treatment of rare genetic diseases, but it also faces technical, ethical and regulatory challenges. Through continuous research and innovation, gene editing technology is expected to bring more treatment options and hope to patients with rare diseases in the future.

6. Conclusion

Gene editing technology, especially CRISPR-Cas9 system, has shown great potential in the treatment of rare genetic diseases. It provides the possibility to cure the disease from the root by accurately locating and modifying the pathogenic genes. However, gene editing technology still faces many challenges. Technically, problems such as the off-target effect, delivery efficiency and long-term safety still need to be solved. In ethical and social aspects, the application of technology involving genetic changes has broken through the traditional ethical boundary, which may lead to moral panic and uneven distribution of medical resources. At the regulatory and legal levels, the existing framework is difficult to meet the needs of rapid development, and the division of responsibilities and legal conflicts in transnational experiments have also increased complexity. In the future, with the continuous maturity and improvement of technology, gene editing technology is

expected to be applied in the treatment of more rare diseases, reduce costs and benefit more patients. However, it is necessary to further study and verify its safety and effectiveness, properly solve ethical problems, promote the popularization of technology and interdisciplinary cooperation, and formulate corresponding regulatory policies to ensure the rational application and management of technology.

References

[1] Qu P, Li X, Liu J, et al. Application of Gene Editing Technology Based on Targeted Delivery Materials in TNBC. ACS omega, 2025, 10(37): 42110-42126.

[2] Xie Y. Research progress in gene editing technologies and their applications in aging-related genes. Journal of Food Science, Nutrition and Health, 2025, 4(1): 82-89.

[3] Ge L, Xiong H. Advances in CRISPR-Cas9 genome editing for the treatment of muscular dystrophies. Chinese journal of pediatrics, 2025, 63(7): 809-812.

[4] Li X, Gao Y, Zhang Z, et al. Biosafety considerations triggered by genome-editing technologies. Biosafety and Health, 2025, 7(3): 141-151.

[5] Sahin N G, Seli E. Gene editing using CRISPR-Cas9 technology: potential implications in assisted reproduction. Current opinion in obstetrics & gynecology, 2025, 37(3): 141-148.

[6] Maj D, Górka K. Applications of CRISPR/CAS9 Technology in Mice and Livestock Genome Editing: Current Research. Annals of Animal Science, 2025, 25(2): 467-481.

[7] Liu D, Cao D, Han R. Recent advances in therapeutic gene editing technologies. Molecular therapy : the journal of the American Society of Gene Therapy, 2025, 33(6): 2619-2644.

[8] Chvileva S A, Yunusova M A, Pristyazhnyuk E I, et al. Generation of iTAF1-36-H8.1 and iTAF1-36-H8.2 Human-Induced Pluripotent Stem Cell Lines with HAR Deletion in the CNTN6 Gene by CRISPR/Cas9 Genome-Editing Technology. Russian Journal of Developmental Biology, 2025, 55(5): 296-306.

[9] Bolideei M, Barzigar R, Gahrouei B R, et al. Applications of Gene Editing and Nanotechnology in Stem Cell-Based Therapies for Human Diseases. Stem cell reviews and reports, 2025, 21(4): 1-30.

[10] Sumner J C. Presymptomatic Treatment of a Genetic Disease with a Small-Molecule Drug. The New England journal of medicine, 2025, 393(7): 714-717.

[11] Jonker H A, Tataru A E, Graessner H, et al. The state-of-the-art of N-of-1 therapies and the IRDiRC N-of-1 development roadmap. Nature Reviews Drug Discovery, 2024, 24(1): 1-17.

[12] Singh S L, Iqbal G, Singh A, et al. The Impact of Next-generation Sequencing on Biotechnology: A Review of Current Applications. Journal of Scientific Research and Reports, 2024, 30(11): 91-97.

[13] Gao L, Bhattacharyya A, Beers B, et al. Pharmacokinetics and pharmacodynamics of PTC518, an oral huntingtin lowering splicing modifier: A first-in-human study. British journal of clinical pharmacology, 2024, 90(12): 3242-3251.

[14] Taibi T, Cheon S, Perna F, et al. mRNA-based therapeutic strategies for cancer treatment. Molecular therapy : the journal of the American Society of Gene Therapy, 2024, 32(9): 2819-2834.

[15] Sato A, Watanabe D, Saito Y. Growing knowledge impact of gene-editing technology on public acceptance: a longitudinal analysis in Japan. GM crops & food, 2024, 15(1): 411-428.

[16] Popova V J, Bets D V, Omelina S E, et al. Adapting Mouse Genome Editing Technique from Scratch Using in utero Electroporation. Molecular Biology, 2024, 58(6): 1312-1320.