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Precision Breeding of Cotton Using Haplotypes and Genome Editing Tools

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Abstract Cotton, as one of the world's most important fiber crops, requires precision breeding strategies to meet the growing demands for yield, quality, and sustainability. This study focuses on the integration of haplotype-based methods and genome editing tools as innovative approaches to accelerate cotton genetic improvement. First, we discuss the definition, identification, and application of haplotypes in resolving complex traits; second, we outline genome editing systems, particularly CRISPR-Cas technology for modifying specific gene targets in cotton. This study emphasizes the synergistic effect of haplotype information and genome editing as a means to validate candidate gene function and shorten breeding cycles. A case study demonstrating the application potential of these precision tools in improving fiber quality is presented. While exploring challenges such as technological limitations, regulatory hurdles, and data integration, this study predicts that emerging advances in pan-genome analysis, graph-based haplotype analysis, and next-generation editing platforms will establish robust processes for sustainable cotton breeding and genetic innovation.

Keywords Cotton breeding; Haplotypes; Genome editing; CRISPR-Cas; Precision agriculture

1 Introduction

Cotton (*Gossypium* spp.) is almost present in everyone's life, from clothing to industries. It is not only the core of the global textile industry but also feeds countless families. However, this seemingly stable crop is facing multiple predicaments: the climate is becoming unpredictable, the threat of pests and diseases is intensifying, and the market is constantly urging higher yields and better fiber quality (Thangaraj et al., 2024). In the past, people believed that traditional breeding could solve these problems. Indeed, it has brought about many successful cases, but as time went by, this approach became increasingly cumbersome. The long breeding cycle, the complex polyploid genome, and the narrow genetic basis of superior varieties have made the "ideal trait" a difficult goal to achieve quickly.

The polyploid characteristics make the genes of cotton like a book that has been rewritten repeatedly, redundant and complex. It often takes researchers several years to identify the key genes that determine yield or stress resistance. Slow phenotypic selection and low genetic diversity make the pace of improvement seem heavy (Sreedasyam et al., 2024). Under the dual pressures of climate and market, it is clearly unsustainable to continue relying on traditional means. The pace of breeding has long been out of step with the rhythm of environmental changes.

Fortunately, the development of genomics has brought new breakthroughs to this field. By identifying haplotypes, that is, specific combinations of superior genes at adjacent gene loci, scientists can more clearly see the "genetic puzzle" that determines agronomic traits (Khalilisamani et al., 2024). This not only makes molecular marker-assisted breeding more targeted, but also makes precision breeding a reality. Meanwhile, the emergence of genome editing technology, especially the CRISPR/Cas system, has provided researchers with a tool that can directly "rewrite" genes (Khan et al., 2023). Genetic improvement that used to take many years now has the opportunity to be accomplished in a shorter period of time. When haplotype analysis is combined with genome editing, breeders are no longer just passively screening but can actively design. They can directly superimpose beneficial genes on superior germplasm to create new varieties that are both high-yielding, high-quality and stress-resistant.

This study aims to sort out the current progress of haplotype research and genome editing in precise cotton breeding, discuss the bottlenecks of traditional methods, the role of haplotype selection, and the latest breakthroughs in editing technology. At the same time, we will also pay attention to the challenges that arise during the combination of the two, whether in terms of technology, regulation, or future development direction. The answers to these questions may be determining the sustainability of the cotton industry in the future.

2 Haplotype-Based Approaches in Cotton Breeding

2.1 Definition and significance of haplotypes

In genetic research, the term "haplotype" may sound a bit academic, but its meaning is actually quite straightforward. It refers to a set of gene variations on chromosomes that are inherited from the same parent due to their close proximity. For breeding, it does not "point points" like individual SNPS, but regards a string of variations connected together as a whole (Bhat et al., 2021). This approach can capture the synergistic effects among multiple genes and is closer to the true genetic picture behind traits than analyzing individual markers alone.

This is especially crucial on cotton. The complex traits of fibers, such as length, strength, and even plant type, are often not determined by a single gene but are the result of the combined efforts of multiple genes. Traditional methods find it difficult to clearly understand this combination relationship, while haplotype analysis can precisely fill this gap. Breeders can thereby more easily identify those combinations that truly have an impact on traits, thereby accelerating the breeding of superior varieties (Sivabharathi et al., 2024).

2.2 Tools and methods for haplotype identification

In the past, identifying haplotypes was a troublesome thing. Now it's different. The popularization of next-generation sequencing (NGS) and high-throughput typing technologies has made all this relatively easy. Different research purposes correspond to different means. For instance, genome-wide association studies (GWAS) are often employed to identify haplotype blocks associated with target traits, relying on a large amount of high-density SNP data (Wang et al., 2022). Another method is called linkage disequilibrium (LD) mapping. It first classifies the relevant SNPS into blocks and then examines the relationships between these blocks and traits (Weber et al., 2023).

Furthermore, the emergence of bioinformatics tools has made work more efficient. Software like Haploview and HaploBlocker can classify haplotypes based on the degree of LD, physical distance, or the proximity of markers. Site-specific amplification fragment sequencing (SLAF-seq) is also often used to discover and type SNPS in order to construct more accurate haplotype structures. Of course, traditional marks have not been completely phased out either. Simple sequence repeat (SSR) markers are still useful in some breeding populations for tracking the genetic flow of specific haplotypes (Wu et al., 2020).

2.3 Applications in cotton trait dissection

When it comes to the usefulness of haplotype analysis, the most direct aspect lies in the analysis of traits. Take fiber quality as an example. Through genome-wide association studies (GWAS) of haplotype blocks, researchers have identified many stable loci and candidate genes related to length, strength and uniformity. This means that when breeding, those "advantageous" haplotypes can be directly selected to improve the quality (Su et al., 2020). The plant type traits also benefited a lot. Haplotype analysis helped reveal the key loci that control plant height, branching Angle and branching length, which is of great significance for mechanized harvesting.

On a more macroscopic level, haplotype mapping enables people to see more clearly the domestication process of cultivated cotton. Some haplotypes in local varieties have shown outstanding adaptability or enhanced traits, and this information provides new clues for variety improvement (He et al., 2021). In addition, with the introduction of genomic prediction models, incorporating haplotype information has also been proven to improve the prediction accuracy of complex traits (Lin et al., 2024). This means that in future breeding decisions, haplotypes will no longer be merely auxiliary information but may become the core basis.

3 Genome Editing Tools for Precision Breeding

3.1 CRISPR-Cas systems in cotton

Among various breeding techniques, CRISPR/Cas9 has almost become a "regular guest". Researchers prefer it not only because of its simple operation and high efficiency, but also because it can simultaneously trigger targeted mutations of homologous genes in allotetraploid cotton. In other words, several related genes can be modified at one time without having to be dealt with separately.

What it can do is far more than just "knocking out" a certain gene. Through CRISPR/Cas9, people can achieve gene knockout, fragment deletion, and even multiple editing, with several modifications carried out simultaneously in a single plant. In recent years, "new members" such as Cas12a (Cpf1) and Cas12b have also been successfully introduced into cotton research (Figure 1) (Wang et al., 2020). They are more flexible in identifying targets, have a lower risk of missing the target, and also have higher editing efficiency. The result is that these genetic modifications can often be stably inherited, and the mutations they produce can also be carried on to the next generation, providing a more controllable approach for the improvement of cotton traits.
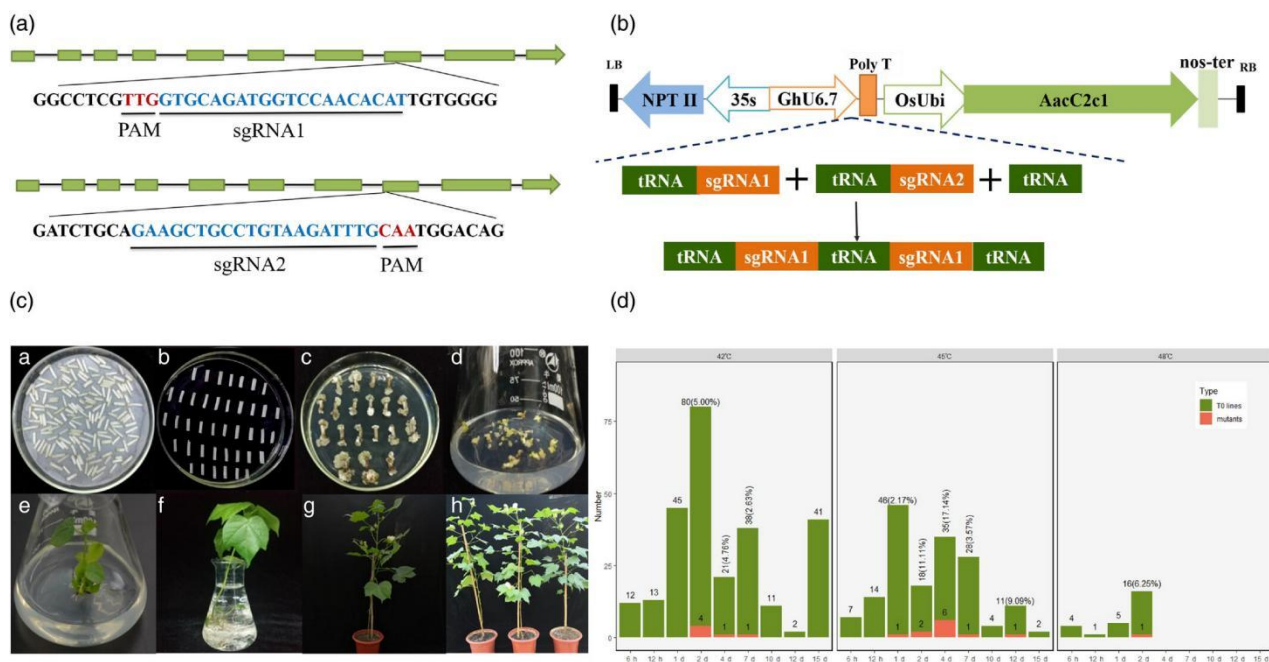

Figure 1 Vector, sgRNAs map, genetic transformation and generated plant through AacCas12b system in cotton. (a) Schematic view of sgRNA1 and sgRNA2 target sites in the *GhCLA* gene. The target sequences are highlighted in blue, and the PAM sites are highlighted in red. (b) Schematic of the T-DNA region of GhRCas12b vector. (c) The *Agrobacterium*-mediated genetic transformation and plant regeneration of transgenic plants. (c-A) Co-culture stage. (c-B-C) Callus induction and differentiation. (c-D) Somatic embryogenesis. (c-E) Plant regeneration. (c-F) The acclimatization of regenerated plant in nutrient solution. (c-G-H) Transgenic plants grown in the greenhouse. (d) Total number of T0 generated plants and the number of positive edits produced under different temperature conditions (Adopted from Wang et al., 2020)

3.2 Delivery methods and transformation protocols

Although gene editing sounds advanced, the step of "delivering the tools into the cells" is not easy. The transformation of cotton has always been a headache for researchers, as it is time-consuming and unstable. The commonly used methods nowadays are still Agrobacterium-mediated transformation or gene gun bombardment, but both of these approaches have their limitations. To bypass these obstacles, some new solutions have been proposed. For instance, apical meristem transformation (SAMT) and virus-induced genome editing (VIGE) have significantly improved editing efficiency and can also overcome genotype-dependent issues (Lei et al., 2022).

In addition, before formal stable transformation, transient expression systems and hair-like root transformation are often used to test the effectiveness of sgRNA (Zhou et al., 2022). Doing so can help detect "invalid designs" in advance and save a lot of time. As for the expression optimization of sgRNA, researchers found that using the

promoter of cotton itself would be more effective. Despite significant progress, the "transformation bottleneck" still exists, which remains a hurdle that must be overcome before the large-scale promotion of gene editing.

3.3 Trait targets modified by genome editing

On cotton, genome editing is no longer just a theoretical attempt; it has been applied to the improvement of various traits. For instance, in terms of fiber quality and yield, researchers have successfully improved textile performance by regulating genes related to fiber length, strength and development. In terms of stress resistance, editing certain genes can make cotton more capable of coping with pressures such as drought, salinity, high temperatures and even pests. Seed quality is also an important direction. The nutritional value of cotton seeds was enhanced by regulating lipid synthesis genes and inhibiting factors related to gossypol (Liang et al., 2020).

In addition, modifications to plant structure and developmental genes, such as plant height, branching, and flowering time, are helping cotton better adapt to mechanization and environmental changes. Some studies have gone further by attempting to edit multiple target genes at one time and superimpose multiple superior traits in the same breed (Hui et al., 2024). Although it sounds like a "combination punch", this is precisely the charm of precision breeding.

4 Integration of Haplotypes and Genome Editing

4.1 Synergy between haplotypes and editing

In the genetic improvement of cotton, haplotypes and genome editing are not two isolated methods. The former is like a precise map, showing the genetic differences behind complex traits. The latter is like a controllable scalpel, capable of precisely "cutting" at the target site. When the two are combined, things become interesting. Haplotype analysis can tell breeders which alleles are worthy of retention or superposition, and editing systems such as CRISPR/Cas can directly "implant" these beneficial combinations into superior germplasm (Peng et al., 2020). This not only avoids the lengthy process of repeated backcrossing in traditional breeding, but also bypasses the constraints of chain burdiness.

Researchers can now even simultaneously improve multiple properties in one round of experiments. Fiber quality, yield, stress resistance, etc. can all be advanced simultaneously (Lyzenga et al., 2021; Kumar et al., 2024). This kind of synergy is not a simple superposition; rather, it is more like the combination of "positioning + precise repair", making complex genetic improvement more directional.

4.2 Functional validation of candidate haplotypes

In the past, finding a "suspect gene" from GWAS or haplotype mapping was one thing, but proving that it was indeed related to traits was another. The emergence of genome editing has made the verification step more straightforward. Through the CRISPR/Cas system, researchers can create mutations, replace alleles, and even fine-tune specific sites to determine whether a certain haplotype truly affects the target trait. The experimental verification of genes related to cotton fiber quality is a typical example. The changes in the traits after editing clearly confirm the conclusion of haplotype analysis.

In addition, the instantaneous expression system and the improved transformation scheme make the verification process more efficient (Ge et al., 2022). Gene functions that used to require several generations of screening to confirm can now often yield results in short-term experiments. In this way, the distance from genomic discovery to breeding application has been significantly shortened.

4.3 Accelerated breeding cycles

For cotton breeding, time is often the greatest cost. Combining haplotype information with genome editing means that "pre-selection" can be carried out in advance at the genetic level, avoiding many detours. For instance, with the assistance of double haploid (DH) induction, researchers can obtain homozygous edited lines within one generation, eliminating the long wait of repeated backcrossing in traditional breeding.

More importantly, with the advancement of multiple editing techniques and genotype-independent transformation systems, even those superior strains that were originally difficult to transform can be rapidly improved (Figure 2)

(Lei et al., 2022). In this way, the research and development of new varieties in response to market or environmental changes can proceed at a faster pace. Overall, this combination makes breeding no longer a "time war", but more like a precise regulation competition, fast, stable and with a clear direction.
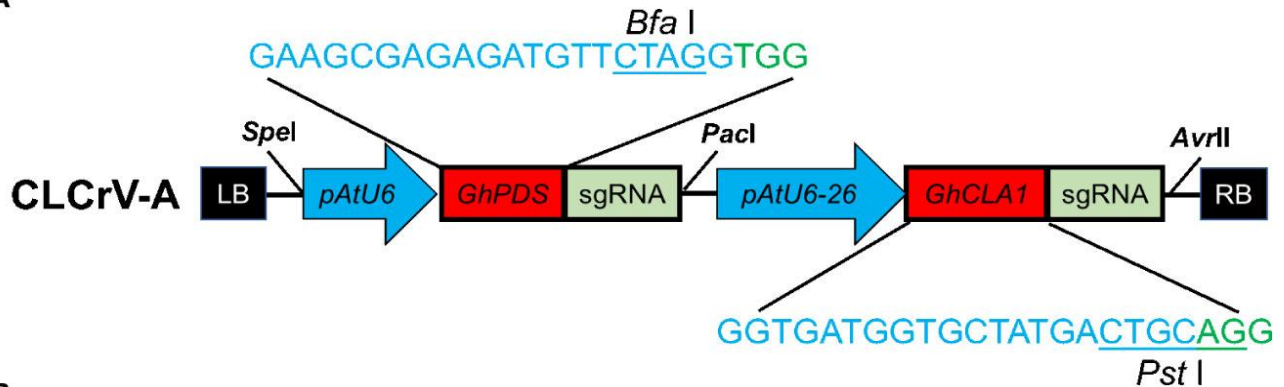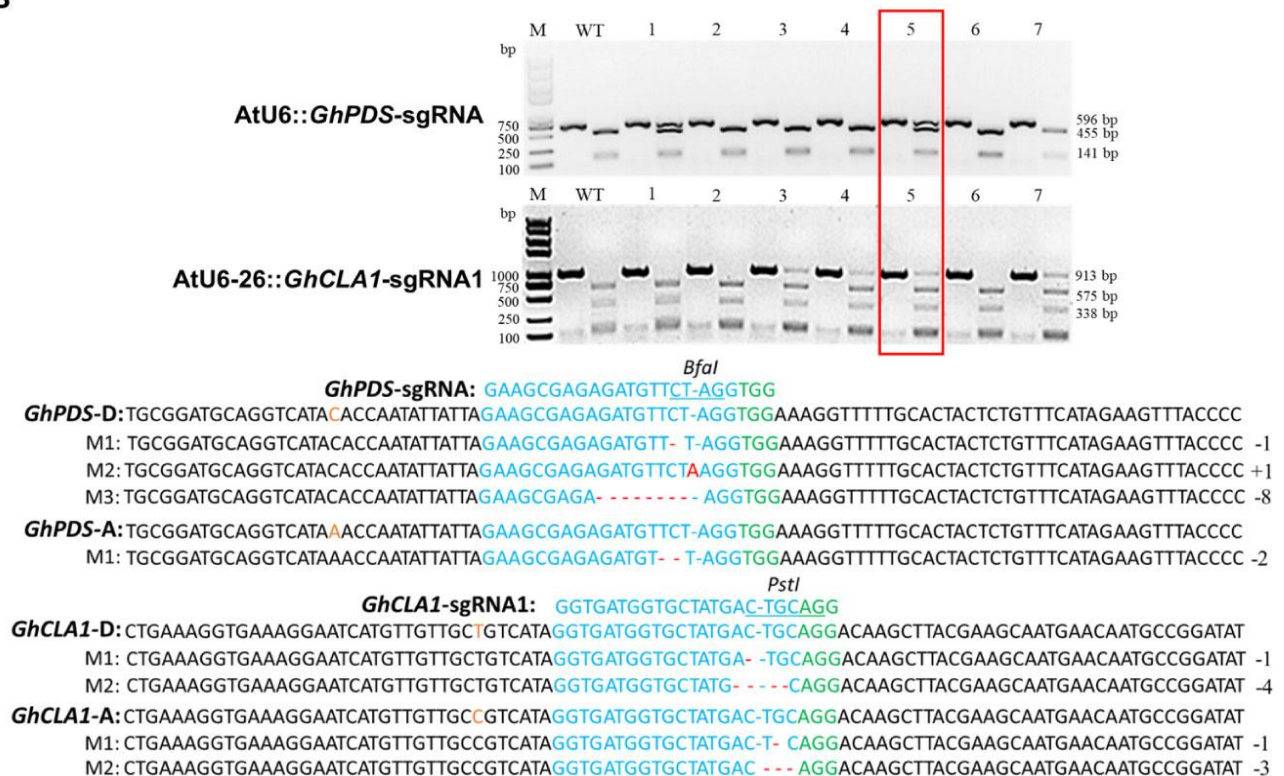

Figure 2 CLCrV-mediated simultaneous editing of *GhCLA1* and *GhPDS* genes in cotton. (A) CLCrV-mediated design strategy for simultaneous editing of *GhCLA1* and *GhPDS*. (B) Detection of *GhPDS*-sgRNA and *GhCLA1*-sgRNA1 targeted double mutations. Wild-type served as a control, and 1-7 were plant numbers. The gel image shows PCR products of the *GhCLA1* gene and *GhPDS* gene, and digested PCR products with Pst I and Bfa I. The undigested PCR products lacking the *Pst* I and *Bfa* I site (due to the presence of a mutation) that were subsequently purified, cloned, and analyzed by sequencing. The red box indicates the double mutation of *GhCLA1* and *GhPDS*. The green color indicates the PAM sequence. The restriction site on the target sequence is underlined in blue. M indicates the mutation sequence. Insertions are denoted with red capital letters. Deletions are shown as red dashes (Adopted from Lei et al., 2022)

5 Case Study in Place: Improving Fiber Quality Using Precision Tools
5.1 Background and breeding objective
One of the most troublesome traits for researchers in cotton breeding is probably the quality of the fibers. Its genetic mechanism is complex and often goes against yield. When the fibers are better, the yield tends to drop (Zhao et al., 2024). This negative correlation has made improving the quality of upland cotton (*Gossypium hirsutum*) a long-standing problem.

In the past, traditional breeding has tried countless methods: hybridization, backcrossing, and screening. However, when both yield and quality had to be taken into account simultaneously, the results were always unsatisfactory. It was not until the concept of precision breeding emerged that people had new ideas. Through means such as molecular markers, haplotype analysis and genome editing, breeders have begun to "find breakthroughs" at the genetic level, attempting to break free from the limitations of traditional methods.

5.2 Precision approach implemented

In recent years, some research teams have attempted to re-analyze and improve the fibrous traits of cotton by using multi-parent hybrid populations in combination with molecular techniques. For instance, by using KASP (competitive allele-specific PCR) labeling, favorable haplotypes can be polymerized at key sites, thereby picking out strains with longer and stronger fibers. Some people have also used GWAS (Genome-wide Association Analysis) and high-density SNP chips to mine candidate genes and verify their relationship with fiber quality, providing a basis for marker-assisted selection and genomic selection.

Some studies have gone even further, no longer stopping at "screening", but directly "taking action". By modifying genes related to fiber development through gene editing or transgenic methods, such as key genes affecting auxin synthesis and transport, researchers have successfully increased both fiber yield and quality simultaneously in some varieties (Chu et al., 2024). Although such attempts are complex, they also provide a practical and feasible path for precision breeding.

5.3 Outcomes and lessons learned

The combination of haplotype analysis and molecular tools has achieved quite remarkable results. The fiber length of many improved series has increased by more than 10%, and the strength has risen by over 17%. What is even more remarkable is that some special allele combinations have broken the long-standing dilemma of "high yield must be low quality", and have cultivated new strains that have both high cotton fiber content and excellent fiber quality. Of course, such achievements were not obtained easily. Genomic selection and marker-assisted breeding do indeed enhance efficiency, but this is only possible if there are reliable molecular markers, solid phenotypic data, and validation of the functions of candidate genes. None can be missing.

Judging from these experiences, relying solely on advanced technology is not enough. Researchers generally recognize that to continuously improve the quality of cotton fibers, it is necessary to integrate multi-omics information, expand genetic diversity, and at the same time, enable traditional breeding experience to work in synergy with modern technology. Precision tools are just the starting point; the key lies in how to make good use of them.

6 Challenges and Limitations

6.1 Technical and biological barriers

The genome of cotton itself is like a maze, huge in size and complex in polyploid structure. It is not easy to operate precisely in such a system. Whether it is haplotype analysis or genome editing, they all have to first confront this naturally complex background. Genetic redundancy is an old problem. A function is often shared by several copies of homologous genes, which makes the design of sgRNA tricky. It is almost a dilemma to be both specific and efficient. The risk of missing the target thus rises, and truly achieving "precise editing" is much more difficult than it sounds.

Besides, not all cotton varieties are "obedient". Many superior strains are difficult to transform. Traditional Agrobacteria-mediated or gene gun methods are inefficient and rely on specific genotypes (Li et al., 2022). In addition, the tissue culture and regeneration steps are time-consuming and labor-intensive, and the entire process often drags on extremely long. Although multiple editing and gene superposition are theoretically feasible, achieving stable inheritance in polyploid cotton still requires further exploration. What can be achieved in the laboratory is still far from being applied in the field.

6.2 Regulatory and public acceptance issues

Beyond technical issues, there are also two "soft barriers" : policy and public attitude. Regulatory standards for genome-edited cotton vary greatly among different countries. Some directly treat it as a genetically modified crop (GMO), while others distinguish between editing and exogenous insertion and offer a more lenient approval process (Saleem et al., 2024). This lack of uniformity has made the commercialization process tortuous. The cumbersome regulatory procedures, the high compliance costs, and the ambiguous definition of intellectual property rights may all slow down the promotion of new varieties.

The acceptance at the public level is not one-sided either. Some people think that genome editing is safer and more accurate, but others remain cautious about the potential environmental and food safety risks. Even though non-GMO editing is theoretically more acceptable compared to traditional genetically modified organisms, the cognitive gap in reality still exists, and the market response thus becomes uncertain.

6.3 Data integration and resource gaps

The success of precision breeding cannot be achieved without high-quality data support, but this is precisely one of the shortcomings of cotton research. Although we already have multiple versions of genomic maps, truly high-resolution and fully integrated reference genomes are still limited. The systematic collection of phenotypic data is also insufficient, and the coverage of label combinations is inadequate. The complexity of polyploid genomes makes data analysis more like "untangle a tangled mess". To identify key haplotypes or pathogenic targets from them requires not only algorithms but also time and computing power.

On the other hand, the insufficiency of computing tools is also slowing down the progress. Stronger algorithmic support is needed in the links of RNA design, off-target prediction and data management. Coupled with the widespread shortage of funds and weak infrastructure in developing regions, many highly promising precision breeding technologies often remain at the laboratory stage (Lassoued et al., 2021).

7 Future Prospects and Opportunities

7.1 Emerging genome editing technologies

In the past, CRISPR/Cas9 was almost synonymous with gene editing; But now, it is no longer the sole protagonist. More and more new platforms are joining this technological race. Tools such as Cas12a, Cas13, base editor, and even lead editor are redefining the boundaries of "precision modification" (Molla et al., 2021).

These systems can do more than just "knock out" genes. They can achieve the replacement of individual bases, simultaneous editing of multiple genes, and even epigenetic modifications. For cotton breeders, this means more flexible means and greater potential for improvement.

Meanwhile, concerns over public acceptance are also prompting researchers to explore alternative approaches. Non-gmo strategies and DNA delivery methods are being actively developed to alleviate regulatory pressure. Coupled with the combination of rapid breeding and genome editing, the process from the laboratory to the field in the future may be significantly shortened.

7.2 Pan-genome and graph-based haplotyping

Cotton research is entering a "pan-genome era". A single reference genome has long been unable to cover all genetic diversity, and pan-genomes and graph-based haplotype maps are changing this situation. Through this new analytical framework, researchers discovered thousands of non-reference genes and presence/absence variations (PAVs), and many key genes that were previously overlooked by traditional methods were re-identified (Li et al., 2024).

What's more interesting is that graph-based pangenomics can not only observe structural variations but also depict complex haplotype relationships. This is of great significance for trait analysis. It enables breeders to more precisely locate the key alleles that affect fiber quality, stress resistance or yield (Jin et al., 2023). In simple terms, this trend is expanding the genetic "material library", providing more abundant resources for future targeted editing and haplotype selection.

7.3 Precision breeding pipelines

In the future, cotton breeding is likely to no longer be a "superposition of individual technologies", but rather a precise system with interlocking links. High-throughput typing, multi-omics analysis, genomic prediction and editing will operate in coordination within the same process. For instance, predictive models established using transcriptome data and gene regulatory networks have demonstrated advantages in enhancing the accuracy and speed of screening superior strains. Meanwhile, GWAS based on functional haplotypes combined with pan-genome resources makes the localization of candidate genes and haplotypes more direct (Li et al., 2021).

When these technologies are fully integrated, the breeding process will no longer rely on lengthy field validation but will be able to rapidly customize new cotton varieties with complex traits at the molecular level (Cheng and Zhang, 2025). In the long run, this systematic and precise breeding is not only aimed at achieving high yields or high quality, but also at ensuring that cotton remains stable and sustainable under climate change and resource pressure.

8 Concluding Remarks

The development of cotton breeding has been advancing rapidly in recent years. When it comes to the key driving forces, haplotype analysis and genome editing technologies, especially the CRISPR/Cas system, have made significant contributions. The old problems that restricted traditional breeding in the past, such as overly long cycles and overly complex trait inheritance, are now being gradually resolved. By targeting and modifying core genes that control fiber quality, yield, stress resistance, etc., researchers have finally been able to manipulate the traits of cotton more directly. Meanwhile, new gene editing platforms, optimized transformation methods, and increasingly mature high-throughput omics technologies are also constantly expanding the boundaries and efficiency of improvement.

However, the real breakthrough does not lie in the individual technologies themselves, but in their integration. Only when genomic data, haplotype information and editing tools can be smoothly connected can the advantages of precision breeding be fully unleashed. Such a system enables breeders to more quickly identify beneficial alleles, verify their functions, and superimpose multiple superior traits onto a single variety. In other words, the path from identification to improvement and then to verification is being greatly shortened. This strategy is not merely about enhancing efficiency; it also gives breeding a stronger sense of direction. It has become feasible to develop "tailor-made" cotton varieties for different environments and market demands.

Of course, the road ahead remains bumpy. Technical barriers still exist, regulatory policies are not uniform, and the public's attitude towards emerging breeding methods remains divided. For these precise tools to truly take root, the joint efforts of scientific research, policies and society are still needed. Despite this, the trend is already quite obvious. Cotton breeding is shifting from experience-driven to data-driven, and from traditional selection to precise design. In the future, cotton varieties that are adaptable, of high quality and more sustainable may no longer be just a concept in laboratories, but a reality in the fields around the world.

Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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