

Research Insight

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Genetic Approaches to Minimize Gluten in Wheat

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Abstract The gluten in wheat is the key to making staple foods like bread taste good. But it is also the main cause of celiac disease and some gluten intolerance diseases. Nowadays, there are many ways to reduce gluten, such as RNA interference, gene editing, mutagenesis screening and molecular marker breeding. Gene editing technologies like CRISPR/Cas9 can precisely knock out or modify multiple copies of the alcohol-soluble protein gene. This can significantly reduce the immune response while still retaining the processing performance of the dough. Researchers have obtained low-gluten wheat strains without genetically modified residues. Methods such as RNAi and TILLING can also lower the level of low-gluten protein and improve the nutritional components of wheat. These improvement measures not only offer celiac disease patients safer choices of staple foods, but also drive the development of healthy foods. In the future, if multi-omics analysis, personalized breeding and synthetic biology can be combined, it is possible to cultivate a new generation of low-gluten wheat that is both safe and delicious. This is precisely the goal of our research.

Keywords Wheat; Gluten; Gene editing; CRISPR/Cas9; RNA interference

1 Introduction

Wheat is one of the world's most important food crops, providing energy and protein for billions of people. It can be cultivated in many regions not only because of its high yield and strong adaptability, but also because gluten protein gives bread, noodles and other foods good taste and processing performance (Sanzan-Leon et al., 2017; Pourmohammadi et al., 2023). Gluten is mainly composed of two types of proteins: gliadins and glutenins. Gliadin makes the dough sticky, while glutenin gives it elasticity. The two work together to form the special properties of wheat dough, which is an important basis for making bread and baked goods (Jouanin et al., 2020).

However, some small fragments in gluten, especially the immunogenic epitopes in α -, γ - and ω -olysin, can cause diseases in some populations, such as celiac disease, non-celiac gluten sensitivity (NCGS), and wheat allergy (Sanchez-Leon et al., 2017; Jouanin et al., 2020; Sharma et al., 2020; Asri et al., 2021). Patients with celiac disease must adhere to a gluten-free diet for life. However, gluten-free foods often require additives, have poor taste and unbalanced nutrition, which makes it difficult for patients to adhere to.

Traditional methods, such as fermentation, enzymatic hydrolysis or physical separation, although they can partially reduce gluten, often damage dough performance and are difficult to completely remove harmful fragments (Jouanin et al., 2017; Pilolli et al., 2019; Sharma et al., 2020). In recent years, genetic improvement has become a research focus. Scientists used methods such as RNA interference (RNAi), gene editing (CRISPR/Cas9), and mutagenesis to silence, knockout or modify the genes of alcohol-soluble proteins and some gluten proteins. The results showed that these methods could significantly reduce gluten content and immune activity while maintaining dough quality to the greatest extent (Sanchet-Leon et al., 2017; Jouanin et al., 2019; Moehs et al., 2019; Jouanin et al., 2020; Asri et al., 2021; Wen et al., 2022; Bennur et al., 2024).

This study will sort out the genetic methods used in the research of low gluten in wheat in recent years, with a focus on the principles and effects of gene editing, RNAi and mutagenesis. It will also discuss their impact on quality and safety, as well as issues related to screening, detection and regulations. Finally, the advantages and disadvantages of different strategies will be compared to explore how to cultivate low-gluten wheat that is both safe and of high quality, providing better staple food options for patients with celiac disease and related conditions.

volume and texture of the bread made are also not good. Therefore, conventional breeding needs to strike a balance between reducing immunogenicity and maintaining the integrity of the gluten network, and also meet the needs of the food industry.

3.3 Use of natural genetic variation within wheat and related species

Wheat and its related species have rich natural differences in gluten composition and the number of immunogenic epitopes. Studies have shown that the immunogenicity of α - and γ -olysin proteins in durum wheat, some wild species and hybrids (such as the wheat-rye hybrid tritordeum) is lower than that in common wheat (Ozuna and Barro, 2018; Pilolli et al., 2019; Marin-Sanz et al., 2023). These genotypes can be used as parents for breeding, and common varieties can be introduced through hybridization or backcrossing, thereby gradually reducing the immunogenicity of gluten. In addition, directed deletion of chromosomal fragments or the use of chromosomal translocations (such as 1BL/1RS rye translocations) can also regulate gluten composition, providing more means for breeding (Pilolli et al., 2019; Marin-Sanz et al., 2023).

4 Modern Genetic Approaches

4.1 RNA interference (RNAi)

RNAi technology can silence some gluten-related genes, thereby significantly reducing the expression of α -, γ - and ω -alcohol-soluble proteins. Studies have found that after RNAi treatment, the gluten content in wheat grains can decrease to 97%, and the stimulating effect of this flour on T cells in patients with celiac disease is significantly weakened, with little impact on dough quality (Altenbach et al., 2019; Garcia-Molina et al., 2019; Jouanin et al., 2019; Sharma et al., 2020). However, because the builders of RNAi remain in the genome, this type of wheat is often identified as genetically modified crops and is subject to regulatory restrictions (Jouanin et al., 2019; Sharma et al., 2020).

4.2 CRISPR/Cas genome editing

CRISPR/Cas9 technology can precisely knock out or modify multiple gluten genes, such as α - and γ -glycolin. Many studies have obtained wheat mutants of low trough protein, whose immune reactivity has decreased by approximately 85%, and some strains have no transgenic residue (Sanchet-leon et al., 2017; Jouanin, 2019; Jouanin et al., 2019; 2020; Liu et al., 2023; Pourmohammadi et al., 2023; Bennur et al., 2024) (Figure 1). CRISPR/Cas9 can also replace some immunogenic epitopes with "safe" epitopes, which can not only improve the quality of bread but also reduce the risk of celiac disease (Jouanin et al., 2020; Liu et al., 2023). However, if gluten is completely knocked out, it may affect the processing performance of the dough. Therefore, a balance needs to be struck between safety and quality (Jouanin et al., 2019; 2020; Liu et al., 2023).

4.3 TILLING (targeting induced local lesions in genomes)

TILLING is a non-transgenic mutagenesis method that uses mutagenesis and then screens to identify mutants of the target gene. TILLING obtained some wheat materials with lower gluten content and weakened immunogenicity on genes such as DEMETER and DRE2 that regulate gluten. These materials can also retain high-molecular-weight gluten subunits, so the processing performance of the bread is basically maintained (Moehts et al., 2019; Wen et al., 2022). However, some mutants may present problems such as decreased pollen viability, which still require further improvement (Wen et al., 2022).

4.4 Transgenic approaches

Transgenic methods involve adjusting the composition of gluten by introducing or silencing specific genes. For instance, introducing wild-type genes into mutants can restore the original phenotype. Alternatively, silencing certain protein subunits with RNAi can also reduce immunogenicity (Vasil and Anderson, 1997; Altenbach et al., 2019; Moehts et al., 2019). Although this method works well in the laboratory, it is limited by public acceptance and policy regulations in practical promotion (Vasil and Anderson, 1997; Altenbach et al., 2019).

5 Case Study: CRISPR/Cas9 Editing of Gliadin Genes in Bread Wheat

5.1 Research background: α -gliadins as key immunogenic proteins

The α -gliadins in wheat gluten contain many immune epitopes related to Celiac disease (CD) and are the main

proteins that cause immune responses in patients. Because of the large number and complex distribution of α -, γ - and ω -olysin protein genes, it is difficult for traditional breeding to remove all immune epitopes (Jouanin et al., 2019; Jouanin et al., 2020; Guzmán-López et al., 2021) (Figure 2).

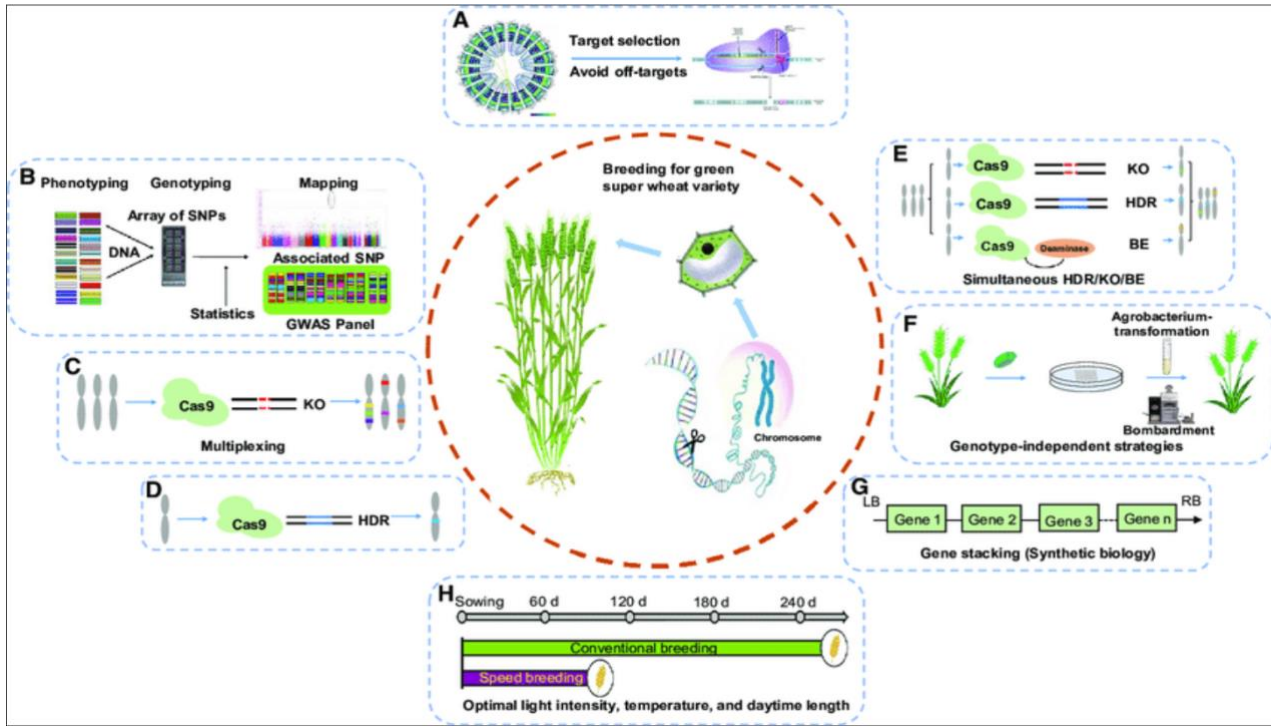


Figure 1 Breeding of a green super wheat variety through CRISPR/Cas9 (Adopted from Bennur et al., 2024)

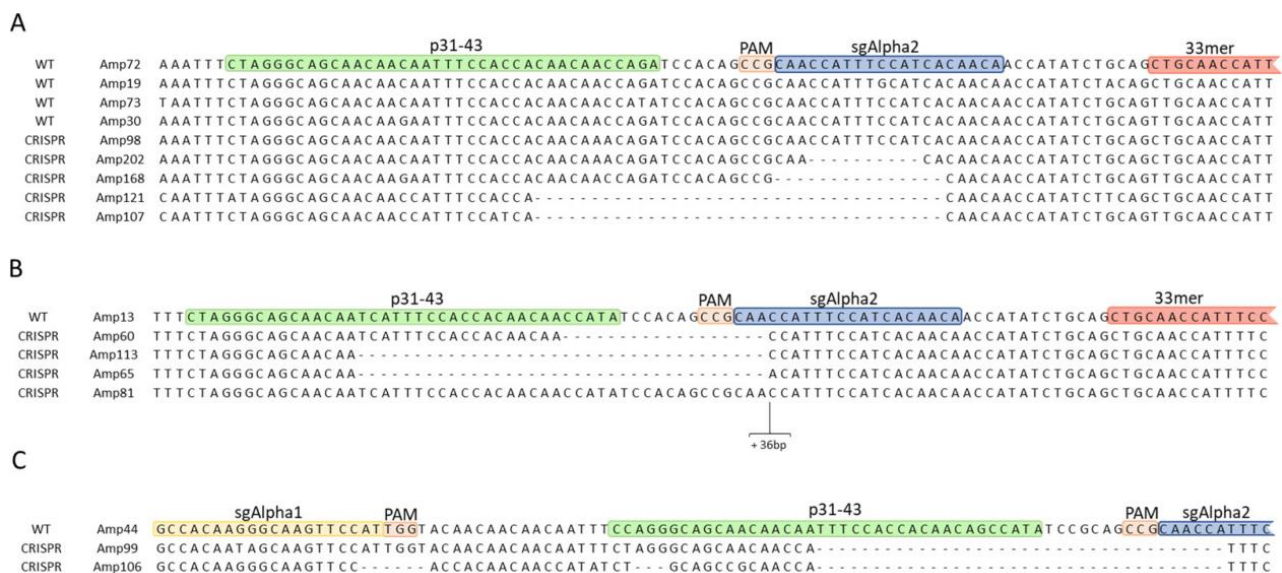


Figure 2 MUSCLE alignment of Amps clusters from the neighbor-joining dendrogram. (A) Cluster 1 of Amps present in lines with DP genotype. (B) Cluster 1 of Amps present in lines with BW208 genotype. (C) Cluster 22 of Amps present in lines with BW208 genotype. DP: Don Pedro. Amps: unique denoised amplicons (Adopted from Guzmán-López et al., 2021)

5.2 Experimental strategy: multiplex CRISPR editing of gliadin gene families

Researchers employed multiple Sgrnas to target the conserved regions of the α -, γ -, and ω -olysin gene families. Through multiple CRISPR/Cas9 editing, they can simultaneously knock out or modify multiple gene copies, thereby significantly reducing the expression of immunogenic epitopes (Jouanin et al., 2019; Guzman Lopez et al., 2021; Yu et al., 2023; Sanchez-Leon et al., 2024).

5.3 Key outcomes: reduction in immunogenic epitopes, retention of acceptable dough properties

The contents of α -, γ - and ω -gliolysis proteins in these CRISPR mutants decreased significantly. In some materials, the total amount of gluten decreased by up to 97%, and the immune epitopes also decreased significantly (Guzmán-López et al., 2021; Yu et al., 2023; Sanchez-Leon et al., 2024). Meanwhile, the edited flour performed normally in terms of dough performance and baking quality, with no obvious problems (Yu et al., 2023).

5.4 Clinical/functional assessment: immunoreactivity tests with celiac patient sera

Serum tests using patients with celiac disease revealed that the immune reactivity of edited wheat was significantly reduced, with some materials showing a decrease of up to 47 times (Yu et al., 2023). In addition, its safety was verified by studies using animal models and T-cell activation experiments (Jouanin et al., 2020; Yu et al., 2023).

5.5 Broader implications: toward gluten-safe wheat lines for commercial production

The multiple editing of CRISPR/Cas9 provides a way to cultivate wheat with low immunogenicity or even "gluten-free". Some editing strains have achieved no transgenic residue and are commercially viable (Liang et al., 2017; Jouanin et al., 2020; Sanchez-Leon et al., 2024). In the future, if high-throughput screening and precise epitope editing are combined, it is expected to obtain "celiac disease-safe" wheat that is both safe and has good processing performance (Jouanin et al., 2019; 2020; Guzmán-López et al., 2021; Yu et al., 2023).

6 Challenges and Trade-Offs

6.1 Maintaining dough quality and baking performance with reduced gluten

Gluten is very important for wheat dough and baking quality. Reducing gluten, especially glycolin, often leads to a decrease in dough elasticity and poor extensibility, affecting the structure and taste of foods such as bread (Gil-Humanes et al., 2014; Sharma et al., 2020). Some studies have obtained low-alcohol-soluble protein wheat using RNAi and found that its dough stability and taste are close to those of common wheat, but it still needs to be optimized to meet industrial demands (Gil-Humanes et al., 2014; Wang et al., 2020). In addition, adding excipients such as low-ester pectin, dietary fiber or polyphenols can partially make up for the deficiency of dough network and improve rheology and texture (Girard and Awika, 2020; Cui et al., 2022; Li et al., 2023).

6.2 Balancing nutritional value (protein composition changes)

Low-gluten protein may alter protein composition, influencing the proportion of amino acids and nutritional value. Some low-alcohol-soluble protein wheat strains have increased contents of essential amino acids such as lysine and higher nutritional value (Gil-Humanes et al., 2014). However, some studies have found that when gluten decreases, the expression of other storage proteins (such as high-molecular-weight gluten subunits) may increase. Therefore, attention should be paid to overall protein quality and digestibility (Gil-Humanes et al., 2014; Nye-Wood et al., 2021).

6.3 Agronomic performance and yield stability

Gluten genes are closely related to agronomic traits such as wheat grain development and yield. Some improved strains showed no significant changes in yield and grain quality after reducing gluten (Landolfi et al., 2021; Buczek, 2024). However, some studies have pointed out that if the gluten level drops too much, it may affect indicators such as grain filling and 1000-grain weight. Therefore, a balance needs to be struck between reducing immunogenicity and maintaining high and stable yields (Wang et al., 2020; Buczek, 2024).

6.4 Regulatory and biosafety issues for gene-edited crops

Gene editing technologies such as CRISPR/Cas are not considered genetically modified in some countries, but policies are not consistent worldwide. Some countries require strict safety assessment and label management, which may affect the promotion of new varieties (Wang et al., 2020; Nye-Wood et al., 2021). At the same time, attention should also be paid to the off-target effects and ecological risks that may be brought about by gene editing.

6.5 Public perception and acceptance

Low-gluten wheat can help patients with celiac disease, but most people do not need a gluten-free diet. The limited acceptance of gene-edited and genetically modified crops by the public, coupled with the sometimes misleading media, may lead some healthy people to blindly choose gluten-free foods, which instead affects nutritional balance (Gil-Humanes et al., 2014; Sharma et al., 2020). Therefore, it is of great significance to enhance popular science publicity and risk communication.

7 Future Perspectives

7.1 Combining genetic editing with breeding strategies

To reduce gluten in wheat in the future, gene editing (such as CRISPR/Cas9) and molecular marker-assisted breeding (MAS) can be combined. First, use CRISPR/Cas9 to knock out or modify the immune epitopes in α -, γ -, and ω -alcohol-soluble proteins. Then, through molecular marker screening and backcrossing, introduce the low trough protein traits into the main cultivated varieties (Jouanin et al., 2019; 2020; Sharma et al., 2020; Wang et al., 2020; Bennur et al., 2024). This combination of multiple methods can maintain both yield and quality simultaneously, and also make up for the deficiencies of a single method, improving the safety and practicability of new varieties (Jouanin et al., 2017; 2019; 2020).

7.2 Toward personalized wheat varieties for different dietary needs

As research on celiac disease and non-celiac gluten sensitivity deepens, in the future, different types of wheat can be developed according to the needs of different groups of people. For instance, wheat without immune epitopes was designed for patients with celiac disease, while some gluten was retained for healthy people to ensure dough quality (Wang et al., 2020; Pourmohammadi et al., 2023). This can make wheat varieties more diverse, meeting both health needs and preserving the taste of food (Jouanin et al., 2017; Wang et al., 2020; Pourmohammadi et al., 2023).

7.3 Advances in multi-omics approaches (genomics, proteomics, immunopeptidomics)

The development of multi-omics technology has greatly accelerated the analysis and functional research of gluten genes. High-throughput sequencing can quickly identify target genes. Proteomic and immune peptide profiling analysis can locate immune epitopes, monitor the effect of gene editing, and also evaluate overall protein changes (Jouanin et al., 2019; Sharma et al., 2020; Wang et al., 2020). These methods provide strong support for screening safe materials and optimizing protein composition (Jouanin et al., 2019; Wang et al., 2020).

7.4 Potential of synthetic biology for novel low-gluten grains

Synthetic biology offers people the opportunity to redesign protein structures and even create brand-new grains. Low protein grains without immunogenicity but maintaining ideal dough performance can be obtained through artificial synthesis or gene reconstruction (Wang et al., 2020; Li et al., 2021). Meanwhile, synthetic biology can also be used to cultivate alternative low protein crops, providing more raw material sources for healthy foods (Li et al., 2021).

8 Conclusion

In recent years, researchers have employed a variety of genetic methods to reduce the gluten content in wheat and lower the risk of diseases such as celiac disease. Common methods include RNA interference (RNAi), CRISPR/Cas9 gene editing, TILLING (targeted mutagenesis), and molecular marker-assisted breeding. RNAi and CRISPR/Cas9 can efficiently silence or knock out α -, γ -, and ω -alcohol-soluble protein genes, significantly reducing gluten content and immune reactivity. TILLING, on the other hand, screens mutants through mutagenesis to achieve non-transgenic trough protein breeding. The progress of molecular markers and genomics has also accelerated the breeding of superior low-gluten wheat strains.

These methods can not only provide safer staple foods for people with celiac disease and gluten sensitivity, but also meet the global demand for healthy food. Low immunogenicity wheat is expected to reduce people's reliance on a strict gluten-free diet and improve the quality of life of patients. At the same time, it can also maintain the processing performance of the dough, facilitating the production of foods such as bread. The promotion of low-gluten wheat will also drive the diversification and innovation of the health food market.

The future improvement direction may integrate multiple technologies, such as multi-genome editing, molecular breeding and multi-omics screening. New tools such as CRISPR/Cas9 are expected to precisely replace or eliminate immune epitopes, maintaining food quality while ensuring safety. Multi-omics technologies (genomics, proteomics, and immunopeptidomics) will help identify safer wheat materials and promote the development of personalized and customized staple foods. Emerging methods such as synthetic biology may also create brand-new low-gluten grains, expanding the sources of healthy food.

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Conflict of Interest Disclosure

The authors affirm 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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