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***REVIEW ARTICLE***

# Molecular and Genomic Insights into Stress Resilience in Cotton (Gossypium spp.)

Junaid Ahmad[1] and Hina Firdous[2*]

[1]Department of Plant Breeding and Genetics, University of Agriculture Faisalabad, Pakistan
[2]State Key Laboratory of Crop Stress Resistance and High-Efficiency Production, College of Plant Protection, Northwest A&F University, Yangling, Shaanxi 712100, China
***Corresponding author:** hinafirdous72@yahoo.com

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## ABSTRACT

Cotton (*Gossypium spp*) as a vital fiber crop in the world is being continually limited due to yield losses caused by increasing abiotic and biotic stresses linked with global warming. The review summarizes recent molecular and genomic developments that have changed our concept of stress resilience in cotton fundamentally. The facets of regulatory architecture of responses to drought, heat, salinity, and pathogen inoculations have been unveiled by the emergence of pan-genomics and multi-omics techniques, such as transcriptomics, proteomics, metabolomics and epigenomics. Families of stress-responsive genes, including heat shock proteins (HSPs), late embryogenesis abundant proteins (LEAs) and aquaporins, NAC, WRKY transcription factors have been well-characterized, with promising areas of crop improvement present in novel gene families including CER (cuticular wax) and PsbX (photosystem II). The high precision of editing these candidate genes has been made possible through functional genomics tools, especially CRISPR/Cas9-based genome editing, which would consequently advance the creation of resilient cultivars. Further on, genomic selection, high-throughput phenotyping and marker-assisted selection are all integrated into breeding pipelines making it easier to transfer molecular findings into elite varieties. Still, issues in functional validation, understanding of multi-stress interactions and application on the field remain. The next generation activities should take advantage of the genetic diversity of wild relatives, apply the systems biology methods, and integrate artificial intelligence to design the next-generation, climate-resistant cotton that would guarantee sustainable production despite increasingly unfavorable environmental factors.

**Key words:** Cotton, stress resilience, multi-omics, genome editing, CRISPR/Cas9, abiotic stress, biotic stress, genomic selection, molecular breeding, functional genomics.

## INTRODUCTION

Cotton (Gossypium spp.) is an economically significant fibre crop which is subjected to constant stresses of abiotic and biotic factors. The increase in pressure on cotton production systems is caused by rapid climate change, soil erosion, salinity spread and development of new pests and insects (Naeem-Ullah et al., 2020). In the last ten years, the genome sequencing, pan-genomics, functional genomics and multi-omics technologies have revolutionized what we know about cotton perception, response, and adaptation to environmental stress (Hina et al., 2024). These improvements give an unprecedented insight into the genome evolution, families of stress-sensitive genes, regulatory networks and the molecular pathways underlining resilience across species and environments (Zuluaga et al., 2023). Combination of comparative genomics, transcriptomics, proteomics, metabolomics and epigenomics has shown multifaceted tiers of regulation of stress tolerance (Roychowdhury et al., 2023). Investigations on wild relatives and diverse germplasm have revealed a wide range of haplotype differentiation, distinctive alleles and lineage-specific expansions of genes, that play a role in thermal, drought, salinity, pathogen, and insect resistance (Majhi et al., 2024). Targeted validation of candidate genes is now being made achievable by using the tools of functional genomics like CRISPR/Cas9, RNAi and VIGS, and the process of molecular breeding, genomic selection and high-throughput phenotyping is speeding up the process of translating these findings into the finished products, which are stress-resistant cultivars (M. K. Razzaq et al., 2021). Nevertheless, even with

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significant advances, there are still critical areas of the functional validation, multi-stress integration, regulatory network resolution and field-level translation (Liang et al., 2025).

In this review, the author seek to provide a synthesis of the existing information on genetic structure, molecular pathways and regulatory processes of the abiotic and biotic stress tolerance in cotton. In particular, the aims are to: (i) to summarise the advances in pan-genomics, comparative genomics and gene family evolution useful in trait adaptation; (ii) combine mechanistic findings using transcriptomics, proteomics, metabolomics and epigenomics; (iii) assess functional genomics and gene-editing technologies driving trait improvement; (iv) also assess the progress made in molecular breeding, genomic selection and field translation. The review, in its ability to combine the evidence to the multi-layers across species, stresses and technologies, offers a multi-purpose, most up-to-date framework to support future functional validation, system-level studies and design of climate-resilient cotton growths. An integrated overview of the molecular, genomic and breeding strategies contributing to stress resilience in cotton is presented in Figure 1, summarizing the major biological layers involved in adaptive responses.

## Genomic Architecture of Stress Responses in Cotton

Cotton has high genomic plasticity, which is the basis of its ability to change to other environmental stresses. Genomic architecture modulates the structural genome composition in addition to the selection of the functional repertoire of the stress-responsive genes (Manivannan & Cheeran Amal, 2023). Polyploidization events, which have allowed allotetraploid cotton species to gain such as *G. hirsutum* and *G. barbadense* to be abundant in gene redundancy, have been utilized to generate raw material in the evolution of new stress-adaptation mechanisms. Comparative genomics have revealed that the polyploid cotton genomes have biased expression of the subgenome with A-subgenomes genes playing more active roles in fiber growth and abiotic stress response, whereas D-subgenomes genes play more active roles in biotic stress response and regulation signaling. The subgenome functional specialization makes the expression of genes be coordinated and specific to stress. Additional mechanisms of stress resilience include structural forms, copy number variations (CNVs) and transposable element activity which are used to adjust gene expression, produce allelic variation and to influence regulatory networks (Dong et al., 2022). In addition to that, pan-genomic analyses have shown that dispensable and lineage-specific genes often encode stress-responsive functions, which highlight the adaptative importance of genomic diversity in cotton. All this gives a guideline to the identification of candidate genes, prediction of their functional consequences, and direct breeding approaches (Zenda et al., 2021).

## Genome evolutionary development and polyploidy

There are more than 45 species of Gossypium genus, and four of these species are independently domesticated. The emergence of allotetraploid upland cotton (genome AADD) was due to the hybridisation of an A genome diploid (probably an extinct A 0 species) with a D genome diploid (*G. raimondi*)(Hu et al., 2021).Such an event of polyploidisation raised genome size, encouraged gene redundancy and provided the potential of neofunctionalization and subfunctionalization of stress related genes. Cotton genome is of great diversity; three major diploid clades have been discovered: African Asian (A, B, E, F), Australian (C, G, K) and New World (D) (X. Li et al., 2024). The relatives of these clades in the wild possess alleles of drought, saline and pest resistance. Recent developments in long read sequencing have generated reference genomes of 19 species and 41 assemblies), and are now able to perform comparative genomics and pan genomics studies (Simko et al., 2021).

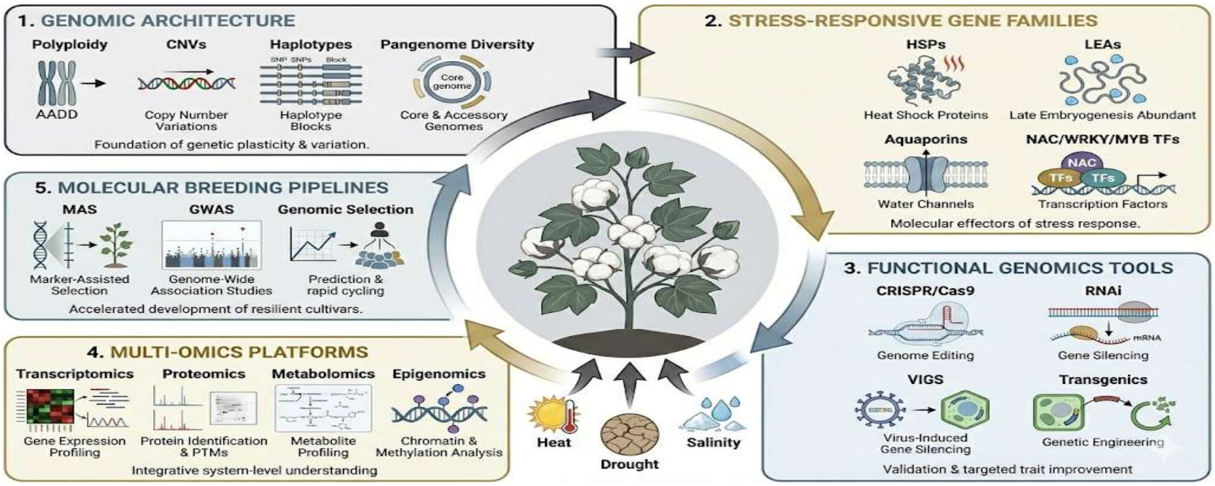

**Fig. 1:** Multidimensional framework integrating genomic architecture, multi-omics platforms, and functional tools to decipher abiotic stress mechanisms in Gossypium spp.. This cyclical workflow accelerates the development of climate-resilient cultivars by translating fundamental molecular insights into precision breeding strategies.

### Pan genomics and diversity of haplotypes

Pan genomic studies give insights into the essential and non-essential genes in cotton species. G. arboreum, G. herbaceum, G. thurberi, G. australe and other diploids have been sequenced and millions of SNPs and structural variants have been identified (Khidirov et al., 2023). In the 3K TCG resequencing project of accessions exceeding 3,200 in tetraploid, 6.7 million SNP and 0.94 million indel SNPs were identified. These variations were translated into high density SNP arrays (80 K, 63 K and 40 K) which make the discovery of candidate genes and genomic prediction faster Genome wide association studies (GWAS) and analysis of haplotype have identified elite haplotypes that are related to drought tolerance, fibre strength and disease resistance (Kumawat et al., 2022). As an example, a peroxiredoxin gene and a putative callase synthase were intro-injected into upland cotton to make the plant drought-resistant and enhance fibre strength.

### Comparative genomics and the wild species

Compared genomics of domesticated and wild cotton species offer information on stress adaptation. The *G. arboreum* and *G. herbaceum* (old world diploids) are pest resistant, early flowering and drought tolerant(Waghmare, 2022). In 375 *G. arboreum* accessions, GWAS revealed 98 loci associated with such traits as fatty acid composition and Fusarium wilt resistance. Segmentation of *G. thurberi* enhanced the quality of the fibres and resistance to stress. Pan genomic studies have further been used to identify stress responsive gene family expansions species specific to species (e.g. heat shock proteins, aquaporins and transcription factors) which could be used to explain adaptive divergence. It is thus necessary to explore genetic diversity of wild species in order to expand the genetic base of cultivated cotton (Han et al., 2022).

### Candidate gene families

Various families of genes are involved in cotton stress tolerance. The heat stress is determined by heat shock proteins (HSPs) and small HSPs that are protecting protein folding and membrane stability. The proteins that accumulate during dehydration are late embryogenesis abundant (LEA) proteins which stabilise proteins and membranes (Khan & Shahwar, 2020). The movement of water and root hydraulics during drought is facilitated by aquaporins. NAC, DREB, WRKY, MYB, bZIP and ERF are examples of transcription factors families that control downstream stress responsive genes. Genome wide identification studies have identified these families and pointed out their growth in *G. hirsutum* compared to that of the diploids. As an illustration, the Eceriferum (CER) gene family, which takes part in the cuticular wax biosynthesis, has 52 members among four cotton species. The localisation of CER proteins is predominantly to the plasma membrane and a few of the genes (e.g., GhCER15D, GhCER04A) are highly induced in drought stress. Photosystem II (PsbX) low molecular weight subunit is also expressed as a small gene family; ten GhPsbX genes were found in *G. hirsutum*, and the gene expression is responsive to salt, high light and drought stresses. The other candidate gene families that play a role in stress adaptation are the voltage dependent anion channels (VDACs) in mitochondrial signaling where 18 GhVDAC genes have been identified and promoters are enriched with hormone and stress responsive cis elements (Hamid et al., 2024a). A concise summary of key stress-responsive genes reported in cotton under heat and drought conditions is provided in Table 1, highlighting their functional roles and molecular pathways.

### Mechanisms in Molecular Tolerance to Abiotic Stress

Abiotic stresses, such as heat, drought, salinity, osmotic stress, cold are coordinated by a complex

**Table 1:** Major stress responsive gene families in cotton

| Gene family | Function in stress tolerance | Key insights and references |
|---|---|---|
| Heat-shock proteins (HSPs) | Molecular chaperones that prevent protein denaturation and assist refolding; maintain membrane stability under heat stress | HSPs and heat-shock transcription factors are up-regulated during heat stress and contribute to thermotolerance(Vierling, 1991) |
| Late embryogenesis abundant (LEA) proteins | Hydrophilic proteins that stabilise membranes and proteins during dehydration; accumulate under drought and cold | LEAs are induced by ABA and DREB pathways; overexpression enhances drought and salinity tolerance(Tunnacliffe & Wise, 2007) |
| Aquaporins | Transmembrane channels facilitating water movement and maintaining cellular water balance; regulate root hydraulic conductivity | Aquaporin genes show differential expression under drought; PIP and TIP members contribute to water uptake and transpiration control(Chaumont & Tyerman, 2014) |
| CER (cuticular wax) genes | Enzymes involved in cuticular wax biosynthesis; modulate non-stomatal transpiration and protect against abiotic stresses | Genome-wide analysis identified 52 CER genes; *GhCER04A* enhances drought resistance by increasing wax deposition(Hamid et al., 2024b) |
| PsbX gene family | Small transmembrane proteins in photosystem II involved in quinone binding and photosynthetic efficiency | Ten *GhPsbX* genes were identified; expression is regulated by salt, high light and drought, indicating a role in abiotic stress responses(Raza et al., 2024a) |
| VDAC genes | Voltage-dependent anion channels on the mitochondrial outer membrane; mediate ion transport and stress signaling | 18 *GhVDAC* genes show diverse motifs and promoter cis-elements responsive to hormones and stress(Akram et al., 2025) |
| NAC, DREB, WRKY, MYB transcription factors | Transcription factors that regulate suites of stress-responsive genes across ABA-dependent and independent pathways | DREB and NAC TFs regulate drought and salt responses; WRKYs and MYBs modulate biotic and abiotic stress crosstalk(Nakashima et al., 2009) |

interaction of physiological, biochemical, and molecular processes to the response of cotton (Patil et al., 2024). The perception of stress involves signal transduction pathways involving hormonal, redox and transcriptional regulation to preserve cellular homeostasis and safeguard critical processes. The efficacy of tolerance mechanisms depends on the severity, timing and duration of stress as well as the stage of development of the plant. Adaptive responses are organized by multi-layered regulatory networks, comprising transcription factors, stress-responsive proteins as well as metabolites and epigenetic modification enables stress memory and priming. Knowledge of these processes gives a basis on the identification of candidate genes, designing stress-resistant cultivars, and applying molecular knowledge in breeding pipelines (M. K. R. Khan et al., 2023).

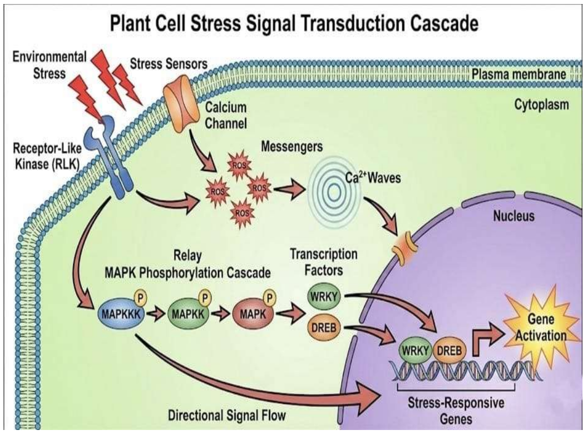

**Fig. 2:** Signal transduction pathways governing plant stress adaptation; This schematic illustrates the cascade from stress perception by plasma membrane receptors (RLKs) to the activation of $Ca^{2+}$/ROS messengers and MAPK phosphorylation relays. These signals induce nuclear transcription factors (e.g., WRKY, DREB) to drive the expression of stress-responsive genes.

### Heat stress

Cotton production is endangered by global warming and frequent heat waves. High temperatures affect photosynthesis, carbohydrate metabolism, hormonal signal transduction and reactive oxygen species (ROS). Heat stress decreases the height of the plant, the number of sym podial branches, boll set, ginning out turn and staple length (Ahmad et al., 2020). An increase in temperature (per degrees Celsius) may decrease crop output by more than 17 percen. Heat stress physiologically causes protein denaturation, membrane destabilisation and calcium homeostasis perturbation (Peer et al., 2020). HSFs stimulate the expression of HSPs, the chaperones and antioxidant enzymes of superoxide dismutase and catalase. GhiHSF21 and GhiHSF14 up regulation and down regulation respectively in cotton are associated with thermotolerance(Zahid et al., 2016). The heat tolerance of transgenic lines has been enhanced by the engineering of HSFs or overexpressing small HSPs. Genome wide association studies have discovered heat tolerance loci; e.g. pollen viability and boll set during heat stress are dependent on allelic variation in GhSUT sucrose transporters (Fragkostefanakis et al., 2014). Heat responses are regulated by epigenetic modifications. The expression of HSF and HSP genes is regulated by DNA methylation and histone acetylation; heating may cause effects on transient modifications of methylation states that provides the memory of previous exposures to heat. The heat responsive genes are also regulated by non coding RNAs (miRNAs, lncRNAs) that influence the stability of the mRNA and translation. Combining the data with epigenomics, transcriptomic, and proteomic will demystify the networks of regulation of thermotolerance(Jha et al., 2020; Zhao et al., 2020).

### Drought stress

It is claimed that drought is the most disastrous abiotic stress to cotton that can cover up to 45 per cent of agricultural land. Water shortage causes loss of photosynthesis, stomatal conductance, cell expansion and nutrient transport, and yield losses of 34 or greater(Bhattacharya, 2021). It is projected that climate changes will cause increased drought in the regions by the end of the twenty first century. Cotton is neither very sensitive nor very tolerant in vegetative stage but very sensitive in reproductive stages where drought decreases the number of bolls, boll weight and lint yield (Ul-Allah et al., 2021).

The ABA dependent and ABA independent pathways are associated with drought tolerance. Dehydration leads to the buildup of abscisic acid (ABA) that causes stomata to close, late embryogenesis abundant (LEA) proteins to be expressed, and ABA responsive element binding factors (AREBs) to be activated. DREB/CBF transcription factors act in pathways that are independent of ABA, that is, they activate dehydrins, aquaporins and osmoprotectant biosynthetic enzyme genes. VDAC gene family is involved in mitochondrial signaling in the drought condition; GhVDAC6, GhVDAC11, GhVDAC13 and GhVDAC15 are expressed when the plants are exposed to water lack. Similarly, CER gene family controls the cuticular wax deposition. GhCER04A is also essential in drought resistance through raising the hydration of the tissue (Hamid et al., 2024a).

Root architecture plays an important role in uptake of water. The further penetrations, longer lateral roots and higher levels of aquaporin expressions increase water uptake(Maurel & Nacry, 2020). The hydraulic conductivity is regulated by aquaporins (PIPs and TIPs); the expression of PIP is frequently elevated in the root of drought tolerant cultivars. The genes that control the root growth, e.g. GhNAC72, GhDREB2A as well as GhMYB family members are up regulated during drought (Guo et al., 2022). CRISPR/Cas9 technology has been used to mutate adverse regulators of drought tolerance by genome editing. As an example, GhMORF genes were edited to enhance drought-resilience and the quality of fibres (data not shown). Nonetheless, the use of CRISPR in cotton drought resistance is quite scarce (Guo et al., 2022). The major signaling modules activated under heat and drought conditions including HSF–HSP pathways, ABA-dependent and independent cascades, ROS detoxification, $Ca^{2+}$ signaling and epigenetic regulators are summarized in Figure 2 for clearer mechanistic understanding.

Salinity affects approximately one billion hectares of agricultural land and the cotton yield may fall 50-60% when exposed to the salt stress (Guo et al., 2022). Excessive levels of sodium and chloride ions impair ion homeostasis, lower water potentials and cause oxidative stress. Cotton has been able to withstand moderate salinity through high levels of K +/Na + ratios, which is a result of Na +/H + antiporters (NHX), the salt overly sensitive (SOS) system and high affinity potassium transporters (HKT). Stabilisation of proteins and membranes are achieved through osmotic adjustment through the build-up of compatible solutes - proline, glycine betaine, trehalose (Yancey, 2020). Cotton transgenic which over expressed the Osmotin gene was found to have better salt tolerance and yield. The discoveries of both the CER and PsbX gene families have offered information regarding salinity responses at the genome wide scale. The genes CER affect the composition of cuticular wax; the leaves with low wax levels have the increased rate of transpiration and reduced chlorophyll amount (Shaheenuzzamn et al., 2021). PsbX proteins regulate the binding of photosystem II and quinone. The GhPsbX genes exhibit a differentially expressed gene in leaves, fibre and roots, and induced by salt stress. Under salt stress transcriptome profiling has shown the up regulation of genes that participate in ion transport, ROS scavenging and hormone signaling.

### Cold and other stresses

Cotton is not resistant to cold, chilling (below 15 degC) retards germination, fibre growth slows down and pathogen vulnerability rises. Cold acclimation is associated with the ICE-CBF-COR cascade (Cai et al., 2019a). CBF transcription factors get activated by inducer of CBF expression (ICE) and activate cold responsive (COR) genes that encode LEA proteins, dehydrins and antifreeze proteins. This pathway is regulated by epigenetic changes and cross talk of cold and ABA signalling. General stress responses like drought and salinity are invoked by other stresses like heavy metal toxicity and UV radiation, which initiate the production of ROS and the damage of DNA (Dutta et al., 2018).

### Biotic Stress Resistance: Crosstalk of Molecules and Gene Regulation

Biotic stresses such as pathogens (e.g., Fusarium, Verticillium, Xanthomonas, Alternaria), insects (bollworm, aphids, whiteflies) and nematodes are devastating to cotton. Plant defence is a complex signaling which is mediated by salicylic acid (SA), jasmonic acid (JA) and ethylene (ET)(Kamburova et al., 2022; Kumar et al., 2021). PAMP triggered immunity (PTI) is triggered by recognition of pathogen associated molecular patterns (PAMPs) by pattern recognition receptors. Effector triggered immunity (ETI) is a resistance-mediated (R) protein, with many of them functioning under nucleotide binding leucine rich repeat (NLR) families. Transcriptomic studies have discovered R gene analogs in cotton and showed an up-regulation of pathogenesis related (PR) proteins during infection(Ijaz et al., 2024). The multi faceted defence answer encompasses both the manufacture of phytoalexins, gossypol and terpenoids; strengthening of cell walls by deposition of lignin; and the production of antimicrobial peptides (Tiku, 2018). Cross talk between pathways of SA and JA controls responses towards biotrophic and necrotrophic pathogens. As an example, GhWRKY33-silenced cotton plants showed an improved resistance to Verticillium dahliae and more susceptibility to Botrytis cinerea, which showed antagonistic interactions(Pandey et al., 2016). Biotic and abiotic responses are also hormonally crosstalked with the biotic responses to drought being weakened by altering the balance of JA/SA. Genomic studies have found QTLs between resistance to bollworm, wilt and aphids providing possibilities to build multi resistance gene pyramids. The disease resistance genes and insecticidal proteins have been pyramid with the help of gene pyramiding employing the method of marker assisted selection (MAS) and transgenic technology. An emerging strategy is defence priming which is a process whereby exposure of pathogens or elicitors in the past leads to intensified defence response in future. As an example, it was found that priming cotton with beta aminobutyric acid or jasmonate analogs, improves Verticillium wilt and whiteflies resistance(Liu, 2025). The molecular explanation of priming will help in a lasting resistance devoid of yield penalties.

### Hormonal Signaling and Crosstalk

The plant hormones relationships are complex and non-linear and thus, their behavior may not be easily simulated. (Liu, 2025). Biotic stress responses are regulated by the plant hormone network which involves the combing of external stimuli and internal physiological states. SA mainly responds to defense against the biotrophic pathogens and JA and ET pathways are triggered to respond to the necrotrophic pathogens and chewing insects. Interaction between these pathways enables the defense responses to be fine-tuned; antagonistic interactions between SA and JA can result in the unnecessary use of energy, whereas under-regulation can make the plants susceptible to some pests(Ku et al., 2018). Research in cotton has shown that silencing of transcription factors like GhWRKY33 increases resistance against Verticillium dahliae and makes them more sensitive to Botrytis cinerea, which reduces the benefits of hormonal regulation. Besides that, ABA which has been implicated with abiotic stress regulate defense responses during drought or heat, which provide evidence of an integrative network where abiotic and biotic stress pathways overlap. The concept of hormonal crosstalk is essential in understanding how to develop multi-stress resilient cultivars that do not impact on the yield and fitness (Manzoor et al., 2023).

### Genes of Resistance and Pathogen Recognition

The cotton immune system is based on R genes which mediate ETI by identifying pathogen effectors. Activation of a series of signaling reactions by NLR proteins triggers the hypersensitive response, ROS generation and the deactivation of downstream defense genes(Nabi et al., 2024). Genomic studies have shown that cotton has many R gene analogs and NLR clusters, which usually have a similar location to the QTLs of disease resistance. As an example, the introgression of NLR-rich segments of wild relatives like G. thurberi increases Verticillium and Fusarium wilt resistance without adversely affecting the quality of the fibres. The PR proteins such as chitinases, glucanases and defensins confer an extra system of protection by breaking the pathogen cell wall and preventing the growth of the microbes. Combination of transcriptomic data during pathogen challenge can be used to identify hub R genes and their regulatory interactions, which can be used as targets in gene editing and molecular breeding (Huo et al., 2023).

### Nematode and Insect Resistance

Cotton uses several molecular approaches to herbivorous insects and nematodes. Insecticidal proteins Bt genes (Cry1Ac, Cry2Ab) interfere with the gut epithelial cells of lepidopteran pests, and the combination with endogenous defense genes is shown to increase durability and spectrum of resistance (Razzaq et al., 2023). Herbivores are prevented by secondary metabolites, such as gossypol, terpenoids, and phenolics, which regulate insect feeding. With gene pyramiding and transgenic technologies, Bt can be used together with sucker-insect resistance, e.g. aphids and whiteflies, without negatively affecting the plant fitness (Singh et al., 2021). Nematode resistance Nematode effectors are detected, cell walls are re-enforced, nematicidal compounds are produced, and hormone-dependent defense networks are activated. Multi-omics studies have shown that these responses are controlled by several important candidate genes, such as WRKY, NAC, and MYB transcription factors, protease inhibitor- and ROS scavenger-coding genes (Manzoor et al., 2023; Singh et al., 2021).

### Defense Priming and Systemic Acquired Resistance

Defense priming increases the capacity of the plant to react more efficiently to the latter attacks by pathogens or insects. Scientifically b-aminobutyric acid (BABA) or analogs of jasmonates are examples of chemical priming agents that activate defense responses faster and more intensely with minimal overall fitness costs. Defense priming exists in two phases: a priming phase, where the chromatin of defense-related genes is modified to allow their expression but not to a full extent, and a post-challenge triggering phase, where later biotic stress causes the expression of the defense-related genes in the primed plants to be faster and stronger than in plants not primed. Priming of cotton is effective at preventing Verticillium wilt, whiteflies, and aphids, demonstrating its possible effectiveness in terms of sustainable protection of crops (Manzoor et al., 2023). Molecular studies indicate that priming changes chromatin access, increases the binding of transcription factors, and triggers PR genes and secondary metabolite biosynthesis enzymes. Defensive signals circulate across tissues (SA) mediates systemic acquired resistance (SAR) which is a process controlling defensive response across tissues. The knowledge of such mechanisms will give a chance to integrate genetic resistance with inducible defense mechanisms, making it less dependent on chemical pesticides (Siddiqui et al., 2023).

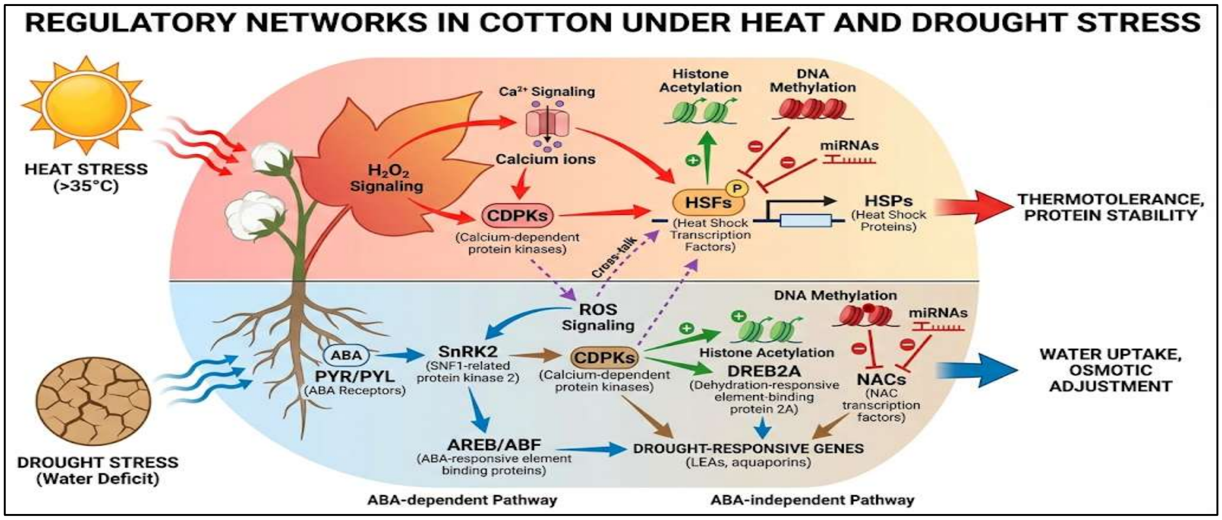

**Fig. 3:** Differential regulatory landscapes governing heat and drought adaptation in cotton; Model integrates hormonal crosstalk and epigenetic modulation with key transcriptional hubs (HSFs, DREB2A), elucidating the distinct molecular pathways driving thermotolerance and osmotic adjustment.3.3 Salinity and osmotic stress.

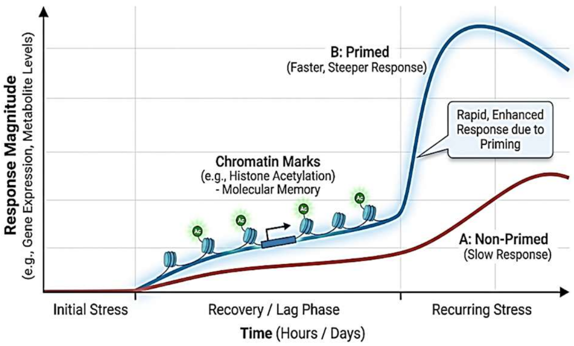

**Fig. 4:** Epigenetic priming and molecular memory in plant stress response; Graph shows that after an initial stress and recovery period, the primed state (B, blue line) exhibits a faster and greater response magnitude (e.g., gene expression) to recurring stress compared to the non-primed state (A, red line). This enhanced response is mediated by molecular memory mechanisms such as retained chromatin marks.

## Multi Omics Deciphering Stress Tolerance

Recent developments of high throughput omics technology have transformed our knowledge on stress resilience in cotton. Conventional physiological and biochemical tests do not give much information about the intricate responses of stress, but with multi-omics methods, genes, transcripts, proteins, metabolites, and epigenetic alterations can all be profiled concerning stress. Using the combination of genomics, transcriptomics, proteomics, metabolomics and phenomics, researchers will be able to detect regulatory hubs, understand molecular pathways, and determine crosstalk between abiotic and biotic stress responses (M. K. R. Khan et al., 2023). This systems understanding is useful in breeding with precision, the functional validation of candidate genes, and the establishment of predictive stress adaptation models. Notably, wild cotton relatives can be characterized using multi-omics techniques which show new alleles and gene networks that can be remodeled into elite cultivars to enhance resilience (Samarasinghe & Lakmal, 2024). A conceptual pipeline illustrating how genomic, transcriptomic, proteomic, metabolomic and epigenomic layers integrate to shape stress-adaptive traits in cotton is shown in Figure 3, providing a systems-level framework for multi-omics interpretation.

## Transcriptomics

The concept of gene expression under stress is highly studied by the use of RNA sequencing (RNA seq). Drought treated cotton seedlings were analysed by transcriptome and upregulation of DREB, NAC and MYB transcription factors; aquaporin genes; and LEA proteins; and downregulation of photosynthetic related genes were found (Chen et al., 2016). The analysis of co expression network and weighted gene co expression network (WGCNA) has found the hub genes that govern the responses to stress. As an illustration, a study of transcriptome and qRT PCR of the CER gene revealed that GhCER15D, GhCER04A, GhCER06A and GhCER12D are induced by water deficit. GhCER04A gene silencing was induced by the virus, that is, the gene was confirmed to play a role in drought tolerance. On the same note, RNA seq in the PsbX assay revealed that GhPsbX genes are tissue specific expressors and are responsive to salinity, intense light and drought (Raza et al., 2024b).

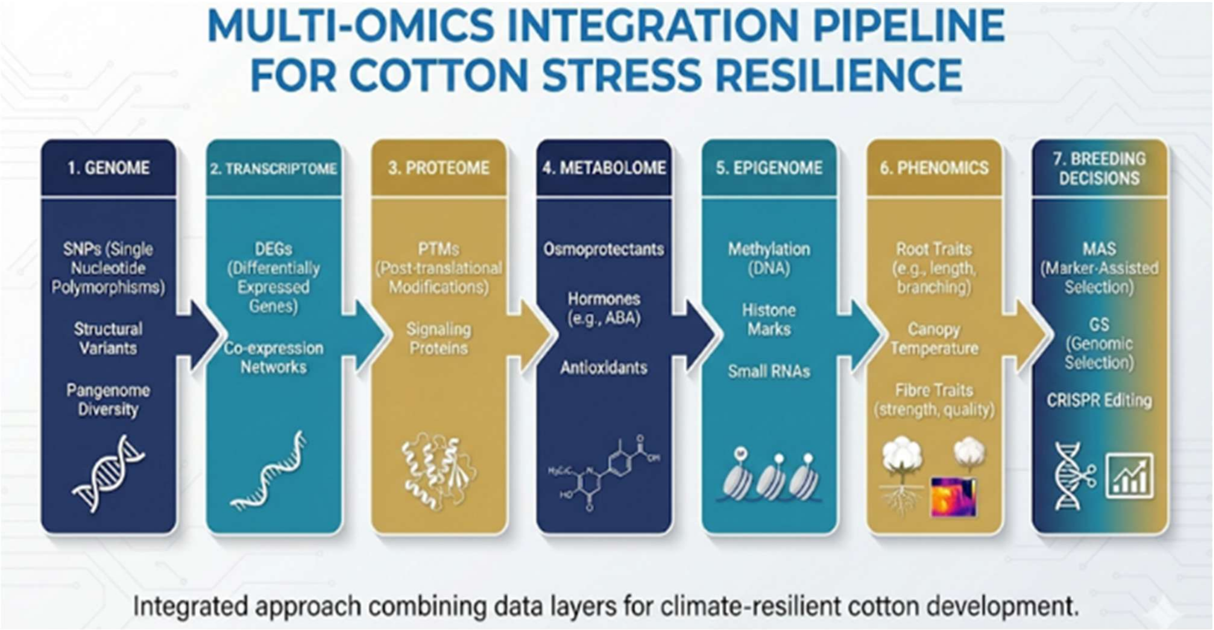

**Fig. 5:** Multi-omics integration pipeline for accelerating stress resilience breeding in cotton; Schematic delineates a systems biology workflow that layers genomic, transcriptomic, proteomic, and phenomic data to precisely identify molecular targets, thereby optimizing marker-assisted and genomic selection strategies for climate adaptation.

### Proteomics

Post translational modifications (PTMs) and changes in abundance at the protein level would be evident in proteomic analyses but would not be evident at the transcript level. Phosphorylation of HSPs, kinases and transcription factors occurs as a result of heat stress. Drought stress manipulates carbohydrate metabolic (e.g. sucrose synthase) and antioxidant defence (peroxidases, glutathione S transferases) and hormonal biosynthetic enzyme concentrations (Olsen & Mann, 2013). Protein turnover is mediated by ubiquitination and stress signaling is regulated by E3 ubiquitin ligases, including GhPUB17, which controls drought tolerance. Stress-induced phospho proteins and quantification of thousands of proteins in the stress response can be accomplished by advanced mass spectrometry methods (e.g., DIA-MS, TMT labelling)(Doroodian & Hua, 2021; Singh et al., 2022).

### Metabolomics

Metabolomics offers a picture of the metabolites being generated as an outcome of the stress. When subjected to drought and salt, cotton accumulates osmoprotectants (proline, glycine betaine), sugars (raffinose, trehalose) and antioxidants (ascorbate, glutathione)(Prakash et al., 2023). The defence against insects and pathogens is provided by such secondary metabolites as gossypol and terpenoids. Interactions of combined stresses may result in either synergistic or antagonistic metabolic responses. Hundreds of stress-related metabolites have been identified using the platforms of gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS). Combining metabolomic data and transcriptomics is used to determine important biosynthetic genes and regulatory centers (Jorge et al., 2015).

### Integrative systems biology and omics.

Integrative analyses most commonly involve more than two layers of omics to form networks of gene-protein-metabolites. Machine learning and network modelling are becoming popular in predicting key regulators as well as ranking candidate genes to be functionally validated(Jorge et al., 2015). In the case of drought tolerance, GWAS in combination with transcriptomics has revealed candidate genes including GhNAC072, GhDREB2A and GhPIP1; these genes exhibit a high level of expression-trait relations. Genomic prediction models that use multi omics data are also used in genomic selection to enhance genomic breeding value estimates. Systems biology methods will be fundamental in the context of multi stress responses and the discovery of crosstalk between signalling pathways (Simmons et al., 2009).

### Cotton Stress Biology in Functional Genomics and Gene Editing

Functional genomics allows one to interrogate the biology of gene functions directly, to reveal the important clues regarding the molecular basis of stress resilience (Joshi et al., 2024). Contrary to the correlative omics studies, functional genomics develops causal relationships between genes and phenotypes. Transgenic techniques, RNA interference (RNAi), virus-induced gene silencing (VIGS), and genome editing methods that use CRISPR/Cas9 are currently in use to understand the role of candidate genes and regulatory pathways in cotton (Kasi Viswanath et al., 2023). This has been achieved by manipulating stress responsive pathways such as ABA signaling, ROS detoxification, cuticular wax biosynthesis and regulation of photosynthesis to produce cotton varieties resistant to stress (Patil et al., 2024). Combining the application of functional genomics with omics-based candidate gene discovery boosts the transfer of molecular understanding in breeding programs (Yang et al., 2021).

### The transgenic and RNAi techniques

Transgenic cotton has been engineered to produce genes that confer drought and salt tolerance (e.g. AtDREB1A, OsHKT1, CIPK kinases) and has been found to be more tolerant in greenhouse and field experiments (Patil et al., 2024). Examples of negative regulators silenced using RNAi have been GhWRKY16 or insect susceptibility genes. Virus-Induced Gene Silencing (VIGS) is fast to validate a candidate gene functionally; silencing GhCER04A decreased cuticular wax and enhanced drought sensitivity (Ahmed et al., 2024). Nonetheless, consumer acceptance and regulatory obstacles restrain commercialisation of transgenic cotton in certain areas.

### CRISPR/Cas9 and improved genome editing

The CRISPR/Cas9 has changed the engineering of plant genomes. The technology involves the guide RNA (sgRNA) to direct the Cas9 nuclease to the target gene, which form double strand breaks and are repaired by non homologous end joining (NHEJ) or homology directed repair (HDR) (Samanta et al., 2016). CRISPR is very specific, efficient and versatile which allows targeted knockouts, gene replacement and multiplex editing. CRISPR/Cas9 in cotton has been applied to produce non transgenic lines that have better fibre quality and resistance against cotton leaf curl virus. Nevertheless, the number of applications aimed at drought resistance is still low and needs additional research (Song et al., 2016). New technologies like base editing and prime editing provide the accuracy that does not introduce a double strand break, providing an opportunity to mutate a point or insert a target in any stress responsive gene. Base Editing is very efficient in the process of small nucleotide polymorphisms (SNPs) (e.g., C to T to make a stop codon) corrections, Prime Editing can be used to do search and replace capabilities, which allows precise insertion or deletion of sequences of DNA. This allows Prime Editing to be especially appropriate in correcting larger structural variants that are related to stress susceptibility (Rasheed et al., 2023). The bottleneck is the development of effective transformation and regeneration procedures with various genotypes of cotton (Saber Sichani et al., 2022). Key examples of genome-edited and transgenic cotton lines that improve abiotic stress tolerance are summarized in Table 2.

### Genetic drives and synthetic biology

Gene drive systems, which are artificial systems designed to preferentially transmit alleles, have potential to be used in cotton although this has yet to be done; they could find use in controlling pests or be used to spread advantageous alleles. Synthetic biology methods are trying to design synthetic gene circuits, which respond to stress signals (Xie & Fussenegger, 2018). As an example, drought or salinity-responsive synthetic promoters would cause expression of protective genes when required, reducing the cost of fitness. The technologies have ethical and environmental issues, yet its ability to provide sustainable pest and stress management is worth considering (Bashor & Collins, 2018; Tang et al., 2020).

## Regulatory Networks and Epigenetic Regulation

Complex regulatory networks that combine transcriptional, post-transcriptional and epigenetic levels of control mediate stress resilience in cotton. These networks enable the quick perception of the environmental cues, fine-tuning of the gene expression and development of stress memory. Signaling interactions among such signaling pathways as ABA, JA, SA, and ROS-mediated networks assist in the coordinated reactions to abiotic and biotic stresses (Mohanta et al., 2018). The accessibility of genes is regulated by the epigenetic processes such as DNA methylation, histone modifications, and chromatin remodeling, which help in long-term adaptation. These networks are highly regulated by small RNAs and long non-coding RNAs (lncRNAs), which regulate transcript stability, translation and chromatin interaction. Knowledge of these regulatory layers is mechanistic and informative of breeding strategies targeted at being precise to breed stress-tolerant cotton (Kesawat et al., 2023; Kumar et al., 2019).

### Small RNAs and post transcriptional regulation

The miRNAs (miRNA), which are also called small interfering RNA (siRNA), regulate the expression of genes through the cleavage of mRNA or translational repression. In cotton, miRNAs are induced by drought against NAC, MYB, and DREB and aquaporin(Jackson & Standart, 2007). As an example, GhCER09A is the target of nine miRNAs (e.g., ghr miR394, ghr miR414d/f), which reminds of the miRNA-mRNA module in the biosynthesis of wax and drought response (Hamid et al., 2024). The hormone signalling and ROS detoxification are also regulated by small RNAs. MiRNA regulatory networks can be understood to identify new targets of gene editing and breeding (Dalmay, 2013).

### Histone modification and DNA methylation

Epigenetic changes like DNA methylation, histone acetylation and histone methylation modify the structure of chromatin and the accessibility of genes. Stress brings about dynamism in these marks and the plants adjust the gene expression and develop stress memory (Kim, 2021; Santos et al., 2017). Drought and heat stress cause genome wide alterations in the pattern of the methylation in cotton. Histone acetyltransferases and deacetylases regulate stress responsive genes expression by modulating the chromatin openness. The interaction between DNA methylation and small RNAs takes place under the RNA directed DNA methylation (RdDM) pathway. Combining epigenomic data with gene expression profiles would enhance the knowledge on the stress induced epigenetic regulation (Wendte & Pikaard, 2017).

### Long non coding RNAs and chromatin remodelling

The SWI/SNF (chromatin remodelling complexes): these act by repositioning the nucleosomes in order to control the expression of genes. Long non coding RNAs (lncRNAs) are able to either recruit chromatin modifiers to a particular locus or to scaffold gene regulatory complexes (Mattick et al., 2023). Recent findings were able to discover hundreds of lncRNAs that were differentially expressed during drought and heat stress in cotton. Other lncRNAs are competing endogenous RNAs (ceRNAs) that trap miRNAs thus de-repressing their target mRNAs. Exploring the lncRNA-miRNA-mRNA networks will help to understand the stress regulation on a greater level(Böhmdorfer & Wierzbicki, 2015; Mishra & Kanduri, 2019).

## Genomic Selection and Molecular Breeding of Stress Resilience

Molecular breeding combines the genomic understanding with the traditional breeding methods to hasten the creation of susceptible cotton cultivars. Through the use of marker-assisted selection (MAS), quantitative trait loci (QTL) mapping, genome-wide association studies (GWAS), and genomic selection (GS), breeders are now able to accurately predict a variety of complex traits including drought tolerance, heat resilience and disease resistance (Yue, 2013). Combined with the multi-omics data, the methods can be used to reveal the specific candidate genes, allele variants, and regulatory networks that are involved in stress adaptation. Molecular understanding implemented in the field-level phenotyping and functional genomics will also guarantee that it is applied to cultivars with better performance across a wide range of environmental conditions (Song et al., 2023).

### Marker aided selection and QTL mapping

In breeding, marker assisted selection (MAS) takes advantage of molecular markers that are associated with quantitative trait loci (QTLs) to breed faster. The loci that have been identified by QTL mapping biparental populations include those that regulate characteristics like canopy temperature, water use efficiency, root traits and fibre quality. G. anomalum and G. thurberi introgression lines provided the QTLs of the drought tolerance and fibre strength (Yang et al., 2023). Genes have been pyramided to confer disease resistance and abiotic stress tolerance using MAS. Nevertheless, the majority of QTLs are small and environment-specific and thus complex traits require genomic selection (Collard & Mackill, 2007). Important QTLs and GWAS-identified loci linked to major abiotic stress tolerance traits are highlighted in Table 3.

### Genomic selecting and predicting models

Genomic selection (GS) involves the use of genome wide markers to make predictions on the breeding value of the individuals without phenotyping them. The GS in cotton is made possible by high density SNP arrays based on resequencing efforts (80 K, 63 K and 40 K arrays)(Desta & Ortiz, 2014). The use of GWAS signals to predict genomes increases accuracy. Multi trait GS models have the ability to select yield, fibre quality and stress tolerance at the same time. The integration of transcriptomic and metabolomic markers augmented by genomic data can be used to produce even more predictive strength (Robertsen et al., 2019). Non linear marker effects and gene-environment interactions are being investigated using artificial intelligence (AI) and machine learning algorithms.

**Table 2:** Representative genome edited or transgenic cotton lines enhancing stress tolerance

| Approach | Target gene(s) and trait | Outcome |
|---|---|---|
| Overexpression of *AtDREB1A* (transgenic) | *AtDREB1A* driven by a stress-inducible promoter for drought tolerance | Enhanced drought and salt tolerance in cotton, but yield penalty under non-stress conditions(Muthurajan et al., 2021) |
| RNAi of *GhWRKY16* (transgenic) | Silencing of negative regulator of drought response | Increased drought tolerance and improved root growth in greenhouse conditions(Wang et al., 2021) |
| VIGS of *GhCER04A* | Silencing of cuticular wax biosynthesis gene | Reduced wax deposition and decreased drought tolerance(Hamid et al., 2024b) |
| CRISPR/Cas9 knockout of susceptibility gene (e.g., *GhCLA1* or leaf curl virus susceptibility genes) | Gene editing for disease resistance | Developed non-transgenic cotton lines with resistance to cotton leaf curl virus(Binyameen et al., 2021) |
| Base editing of fatty acid desaturase gene (*GhFAD2*) | Editing oil composition for nutritional improvement | Produced high-oleic cottonseed oil lines with improved oil quality(Chen et al., 2020) |

**Table 3:** Selected QTLs and GWAS hits for abiotic stress tolerance in cotton

| Trait | QTL/Gene | Discovery method | Notes |
|---|---|---|---|
| Drought tolerance (root length, canopy temperature) | *GhQTL-Dt1* locus | QTL mapping and MAS | Associated with deeper roots and cooler canopy temperature; used in marker-assisted selection(Mahmood et al., 2019) |
| Fibre strength under drought | Peroxiredoxin and callose synthase from *G. anomalum* | Introgression and QTL mapping | Introgressed fragment improved fibre strength and drought tolerance(Xu et al., 2022) |
| Fatty acid composition and wilt resistance | *3-oxoacyl-ACP synthase III* and GSTF9 homolog | GWAS in *G. arboreum* accessions | Associated with palmitic and palmitoleic acid content and Fusarium/Verticillium wilt resistance(Hou et al., 2018) |
| Cuticular wax deposition under drought | *GhCER04A*, *GhCER15D* | RNA-seq and qRT-PCR | Genes show elevated expression under water deficit and regulate wax biosynthesis(Hamid et al., 2024b) |
| Photosynthesis under salinity and drought | *GhPsbX* genes | Comparative genomics and RNA-seq | Expression regulated by salt, high light and drought; may optimise photosystem II efficiency(Raza et al., 2024a) |

**Table 4:** Comparison of Modern Breeding Approaches for Cotton Stress Resilience

| Method | Applications | Limitations | Reference |
|---|---|---|---|
| Marker-Assisted Selection (MAS) | Targeting simple, qualitative traits controlled by one or two major genes (e.g., Bt-mediated insect resistance, monogenic disease resistance). | Effectiveness is significantly reduced for complex, quantitative, or low-heritability traits (e.g., drought tolerance) where multiple minor genes govern the phenotype. | (Misra & Singh, 2025) |
| Genome-Wide Association Studies (GWAS) | Discovering novel candidate genes and QTLs across diverse, unrelated germplasm collections, capturing broader allelic diversity than biparental mapping. | Requires very large population sizes to achieve statistical power; often exhibits reduced power for detecting rare alleles or structural variants. | (Susmitha et al., 2023) |
| Genomic Selection (GS) | Improving complex, polygenic traits such as yield and drought tolerance by predicting Genomic Estimated Breeding Values (GEBVs) without prior phenotype screening.\ | Demands high-density marker data, large and representative training populations, and robust statistical models to maintain prediction accuracy across environments. | (Alemu et al., 2024) |

### Breeding omics pipes: Two-step breeding

There should be strong pipelines between omics discoveries and breeding, which involves marker validation, phenotyping and selection. Multi omics identified candidate genes need to be functionally confirmed by CRISPR or transgenics and subjected to field trials (Mahmood et al., 2022). Phenotyping platforms (e.g., UAV mounted thermal imaging, root imaging) can be used to measure stress traits in a short period of time. The integration of data between phenotypic and transcriptomic and the Genomic data will be instrumental in making a decision on marker prioritisation and selection. Genomic selection models should be able to include the environmental covariates together with climate predictions in order to produce climate resilient cotton (Roychowdhury et al., 2023).

### Case study: drought hardy molecular breeding tools

Molecular breeding tools to improve the drought resilient cotton. They emphasized the employment of QTL mapping, GWAS, transcription factor analysis, transcriptomics and CRISPR/Cas9. Despite the identification of hundreds of QTLs and genes, they have not been functionally validated and translated to the field (M. K. Razzaq et al., 2021). The simplicity and specificity make CRISPR/Cas9 popular, but there is not much use in the area of drought tolerance. Base and prime editing can provide an opportunity to make accurate changes to drought responsive genes (Alharbi et al., 2024). The authors underlined the fact that wild relatives of cotton are abundant sources of new alleles and need to be utilised in breeding programmes of the future.

### Translational Insights: Molecular Discoveries to Field Application

The final ambition of cotton stress biology studies is transformation of the molecular findings into cultivars that are more resilient, yield stable and fiber quality in the real world setting (Patil et al., 2024). Although genomics, functional validation and multi-omics studies can give the understanding of the potential responses of stress-sensitive genes and pathways, their effective implementation would need coordination with breeding programs, field validation and optimal agronomic practices. The purpose of translational work is to the laboratory research and practice: it is important to see that molecular innovations can provide farmers and the global cotton production system with real benefits (Passioura, 2020).

### Field validation of candidate genes

The candidate genes discovered by the use of omics and functional genomics need to be tested in various environments. Transgenic cotton overexpressing AtDREB1A or CIPK6 had been found to have better drought and salinity tolerance in field trials, although stressed conditions were not applied, and yield penalties under non stress conditions indicated that tissue or stress inducible promoters were crucial (Tian et al., 2018). Introgression lines possessing desirable alleles of wild species should be tested in different locations and years to determine stability (Ali et al., 2010). The benefits of gene editing would be the introduction of advantageous alleles into elite cultivars that would not be dragged along by linkage.

### Molecular used in breeding programme

Genotyping Liability The large-scale selection is possible in high throughput. QTL SNP markers of root architecture and water use efficiency and disease resistance are being adopted in breeding pipelines (Abbas et al., 2022). As an example, the GhQTL-Dt1 locus that governs root length has been used to select drought tolerant lines using markers of the locus. Some breeding programmes are currently piloting genomic selection, and the initial findings have indicated faster genetic gain (Rasheed et al., 2017).

### Connection with agronomic practices.

Molecular enhancement and agronomic strategies in the form of conservation tillage, deficit irrigation, mulching, and soil amendments should be employed to make sure that stress reduction will be effective at the field level. Genetic advances that involve field translation necessitate a systemic Genotype × Environment × Management (G×E×M) system whereby superior genotype is implemented in the suitable environments and agronomic management. Even drought resistant cultivars need to have optimum irrigation timelines and soil fertility in order to realize their genetic potential. The sensor-based irrigation apparatus and remote sensing-enabled precision farming apparatus are, in this regard, key components that enhance water-use effectiveness, reduced stress levels, and stabilizing yields in diverse field environments. (Xing & Wang, 2024).

### Case studies

### Drought tolerant Bt cotton

Transgenic cotton lines that have the Bt insect resistance gene as well as the drought tolerance gene (e.g., AtDREB1A) are created and tested under the field environment. Bt insect resistance gene transgenic cotton lines are also produced and tested in the field environment including a drought tolerance gene (e.g., AtDREB1A). Transgenic cotton lines pyramided with Cry1Ac, Cry2A, and Vip3Aa genes were found to be more effective with a fatal effect of approximately 99 percent in relation to mortality of Helicoverpa armigera with a fatality of 70 percent in transgenic lines expressing double Cry toxins alone. Moreover, these pyramided lines retained more boll and expressed more insecticidal proteins (4.23 2g/mL) even in moderate conditions of drought stress, circumventing the yield penalty of single-gene Bt varieties (Shad et al., 2021).

### Introgression lines that are salt tolerant

The upland cotton on which a fragment of *G. anomalum* that contained a peroxiredoxin gene was introgressed enhanced its fibre strength and salt tolerance (Yang et al., 2023). These lines show the way genomic resources may be used to breed.

### Cuticular wax modification

GhCER04A overexpression also led to higher cuticular wax and tolerance to drought (Hamid et al., 2024). On the other hand, VIGS of GhCER04A decreased wax and made them more susceptible, which showed the possibility of water conservation through the manipulation of wax biosynthesis.

### Problems and Future considerations

Candidate genes have been identified in thousands but few have been confirmed. Functional studies will be hastened by developing high throughput CRISPR and VIGS systems of cotton (Yuan et al., 2025). The validation in the field is also crucial whereby greenhouse performance is not always transferred to the field. Majority of the research studies test single stresses, but crops are subjected to compound stresses (ex: heat x drought x salinity). The multi stress experiments and long term field trials are needed to measure synergies and genotype x environment interactions. The pipelines of multi omics integration in breeding are complicated. There is also a requirement of data standardisation, data sharing and computational frameworks. Machine learning can be used in finding predictive markers and network hubs (Hasan et al., 2023).

In cotton, technologies of gene editing (base editing, prime editing, CRISPR/Cas12, CRISPR/Cas13) should be optimised. CRISPR/Cas9 mainly targets DNA to make it permanently modified in the genome, whereas CRISPR/Cas13 specifically targets the RNA molecules, which makes it especially useful in generating immunity to RNA viruses, in which case the viral genome is degraded directly without the introduction of new family genes.Synthetic biology and gene drives, despite being promising, present a biosafety issue and need regulation (Z. Khan et al., 2023). The frequency and severity of the abiotic stresses will keep growing due to climate change. Climate projections must be included in breeding programmes to predict stressful situations in the future (Redden, 2013). Coupling genomic selection and crop growth models with climate data can be used to identify genotypes that have constant performance under anticipated climate conditions. Future studies (Figure 6) ought to center on taking advantage of the genetic diversity of wild species, creation of drought and heat-tolerant cultivars by use of precision breeding, awareness of epigenetic control as well as application of AI-driven instruments in data assimilation and decision support (Muntean et al., 2025). To develop climate resilient cotton systems, there will be a need to work together with geneticists, breeders, physiologists, and data scientists.

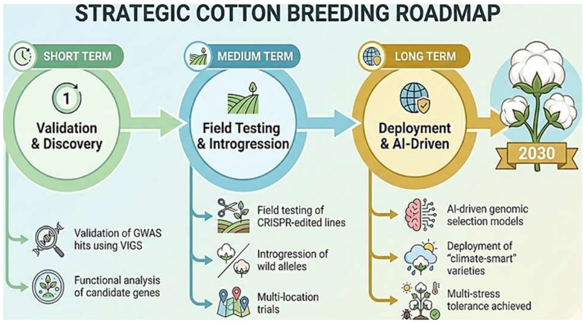

**Fig. 6:** Strategic Roadmap for Climate-Resilient Cotton Breeding in Upcoming Years.

**Table 5:** Key Wild Gossypium Species, their Genome Classification, and Stress-Resilience Traits with Associated Molecular Mechanisms

| Species | Genome Group | Target Trait | Identified Mechanism / Candidate Genes | References |
|---|---|---|---|---|
| *Gossypium arboreum* | Old World Diploid ($A_2$) | Pest resistance; Early flowering; Drought tolerance | Higher constitutive expression of defense genes; variation in flowering-time regulators (FT-like genes); drought response linked to ABA-responsive TFs and osmoprotectant pathways. | (Naqvi et al., 2017) |
| | | Fatty acid composition; Fusarium wilt resistance | 98 GWAS loci identified; candidate genes include GSTF9 (oxidative stress detoxification) and 3-oxoacyl-ACP synthase III (lipid biosynthesis); resistance linked to enhanced basal immunity. | (Gong et al., 2018) |
| *Gossypium herbaceum* | Old World Diploid ($A_1$) | Pest resistance; Early flowering; Drought tolerance | Variation in secondary metabolite pathways (gossypol biosynthesis); photoperiod-insensitive alleles; improved root architecture and stress-inducible transcription factors. | (Yue et al., 2024) |
| *Gossypium thurberi* | Wild Diploid ($D_1$) | Cold stress tolerance | ICE–CBF–COR signaling cascade mediated by CBF4 and ICE2, enhancing membrane stability and cold-responsive gene expression. | (Cai et al., 2019b) |
| | | Verticillium and Fusarium wilt resistance | Introgression of NLR-rich genomic regions encoding disease-resistance proteins; activation of salicylic acid–dependent defense pathways. | (Li et al., 2023) |
| | | Drought tolerance; Fiber strength | Introgressed QTLs affecting fiber cell elongation and secondary cell wall deposition; improved water-use efficiency through stomatal regulation. | (Akhtar et al., 2023) |
| *Gossypium anomalum* | Wild Relative ($B_1$) | Drought tolerance | Enhanced antioxidant defense system and ABA-mediated signaling; introgression segments associated with root vigor and osmotic adjustment. | (A. Razzaq et al., 2021) |
| | | Salt tolerance; Fiber strength | Introgression fragment containing Peroxiredoxin genes (ROS scavenging); improved ion homeostasis and maintenance of fiber cell integrity. | (H. Li et al., 2024) |

## Conclusions

Cotton (Gossypium spp) continues to be one of the backbones of world production but its yield is increasingly under attack due to the increased effects of climatic changes, soil erosion and new pests and diseases. The last ten years saw the most significant change in the study of stress resilience in cotton due to the development of genomics, pan-genomics, and multi-omics technologies. Transcript, proteomic, metabolic and epigenomic analyses have provided an insight into the complex regulatory systems that orchestrate responses to abiotic stresses, including heat, drought, salinity and cold, and biotic challenges, including pathogens and insect pests. HSPs, LEAs, aquaporins, and transcription factors candidate gene families and newly found families, such as CER, PsbX, and VDAC have become the promising targets of functional validation and crop enhancement. CRISPR/Cas9, base editing, and other RNAi-based systems have allowed their easy interrogation and editing of stress-responsive genes, and have made it possible to engineer resilient cotton lines. In the meantime, marker-assisted selection and genomic selection pipelines, which use high-density SNP arrays and multi-trait prediction models, have increased the speed at which molecular knowledge is converted into breeding programs. Nonetheless, difficulties still exist in the translation of laboratory findings to the performance of the field. Multi-stress testing, testing under a wide range of environments, and combining with agronomically optimized practices are important factors to achieve all the potential of genomics-based cotton improvement.

In the future, climate-smart cotton farming can have a radical solution due to the exploitation of the genetic diversity of wild species in combination with precision breeding, sophisticated genome editing, and assists artificial intelligence integrative omics. Knowledge of epigenetic control, stress memory, and regulatory interactions will also help us enhance our capacity to create the cultivars with the desired yield, fiber properties, and resilience to challenging and dynamic stress conditions. It will be necessary to engage in collaborative, interdisciplinary work between genomics, breeding, physiology, and computational biology to develop next-generation cotton varieties capable of supporting the global production of fiber and oil because of the increasing environmental pressures.

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