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REVIEW ARTICLE

Comprehensive review on growth regulating factor (GRF): A transcriptional factor in rice (*Oryza sativa*)

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Abstract

Rice is the staple food for more than half of the world's population. Production is a major consideration for a future-demanding, growing population. Plant growth is mediated by several gene expressions. Growth regulating factor (GRF) is a transcription factor (TF) family member, which includes 12 GRF members in rice. Evolutionary analysis of GRF showed that GRF members were found in all land plants, participate in growth, development, metabolism and are involved in defense mechanisms. In rice, 12 members of GRF are expressed in different tissues at different time intervals and regulate leaf size, stem elongation, floral development, grain size improvement and resistance against biotic and abiotic stresses. GRF has two domains, QLQ (glutamine-leucine-glutamine) and WRC (WRKY rich cysteine). GRF TF interacts with a co-activator called GRF-interacting factor (GIF) and GIF harbors an SNF (sucrose nonfermenting 2) domain. This GRF-GIF duo, along with miRNA (micro RNA), regulates downstream target genes. *miR396* specifically targets GRFs and functions in the repression of specific GRFs and is upregulated during stress conditions. This complex can be regulated by hormones such as gibberellic acid, brassinosteroid, which have a tremendous effect on the expression of GRF genes under normal and stress conditions. Some of the members are novelly present in some varieties and exhibit their expression, like *GS2/GL2* (Grain Size2/ Grain Length2) allele, which regulates grain size. New germplasms harboring GRF function can be created by transgenic approaches, RNAi (RNA interference) methodologies, target mimic approaches and breeding programs. Understanding their structure and function, as well as their regulatory mechanisms across different tissues, can be utilized to target desirable agronomic traits with significant economic value.

Keywords: gibberellic acid; GRF-interacting factor; growth regulating factor; *miR396*; rice

Introduction

Transcription factors (TFs) play a crucial role in regulating gene expression in organisms. Gene expression is controlled at the molecular level by the TF (1). Growth and development and defense mechanisms of the organism are mediated by gene expression regulation through transcription activation or repression. Several transcription factor families that regulate plant development and defense mechanisms have been reported, including Homeobox TFs, KNOX (knotted-related homeobox), WOX (WUSCHEL-related homeobox) and ZF-HD (zinc finger-homeodomain); MADS box TFs, AG (AGAMOUS), AP1 (APETALA1) and LFY (LEAFY); bZIP TFs (basic leucine zipper); MYB TFs (myeloblastosis) and bHLH TFs (basic helix-loop-helix) (2). Rice possesses approximately 2384 transcription factors that come under 63 families (3). One of the important transcription factors, GRF TF regulates gene expression patterns, thereby altering plant growth and development. GRF is a small transcription factor families that regulate plant growth and function, stress response and defense mechanisms.

The first GRF TF, *OsGRF1 (Oryza sativa* GRF 1), was reported in deep water rice (*O. sativa* L.) in the intercalary meristem as a 222 bp cDNA using EST (expressed sequence tag), which shows the properties of a transcription factor found to regulate GA (gibberellic acid) induced stem elongation (4). Further research was carried out to delineate the functions of the GRF TF at the molecular level. The GRF family has an ancient origin from charophyte algae species (*Klebsormidium nitens*) found a single copy of the GRF gene and evolved in land plants likely due to duplication events, selection pressure and expression patterns (5). The GRF family has divergent members ranging from one GRF in *Marchantia polymorpha* (liverworts) and two GRF in *Physcomitrella patens* (moss) to 22 GRF in *Glycine max* (6, 7). In rice, the number of GRF members varies among cultivated and wild rice varieties. *O. sativa japonica* has 12 GRF members, *O. sativa indica* and *O. rufipogon* has 13 GRF members (8-10). In this review, we discuss how GRF genes in rice regulate growth, development and defense mechanisms.

Structure of GRF TF

GRF TF protein size ranges from 20 kDa to 60 kDa it has two conserved domain regions, QLQ and WRC, located at the N-terminal region of the GRF protein (11). The C-terminal region of the protein is highly variable, yet it also contains some conserved regions like FFD (phenylalanine-phenylalanine-aspartic acid), TQL (threonine-glutamine-leucine) and GGPL (glycine-glycine-proline-leucine) (5). This C-terminal conserved region is found only in some GRF families. The QLQ domain is a sequence of 36 amino acids. The QLQ domain comprises glutamine-leucine-glutamine residues (QX_3LX_2Q) and aromatic/hydrophobic and acidic amino acids. The QLQ domain shows similarity with SWI/SNF (switch 2/sucrose nonfermenting 2) in yeast, an ATP-dependent chromatin remodeling complex. SWI/SNF shows similarity to GRF QLQ due to protein-protein interaction activity. This domain in GRF also interacts with transcriptional co-activators called GIF (4, 12). The QLQ domain in both SWI/SNF and GRF has some conserved amino acid sequences apart from the QX_3LX_2Q motif, which include phenylalanine, proline and tryptophan at positions 2, 27 and 30 of the amino acid sequence. The GRF QLQ is said to have evolved from the SWI/SNF QLQ, which exhibits sequence similarity; however, it also displays divergent chemical properties and amino acid charges. The conserved QLQ domain, which harbors two glutamic acids at positions 9 and 11, has acidic amino acids and a negative charge on GFR QLQ, while SWI/SNF QLQ has neutral to basic amino acids and neutral to basic charge (5, 13).

The WRC (WRKY rich cysteine) is the most conserved domain among the 5 mentioned domains (QLQ, WRC, FFD, TQL and GGPL) of GRF. It consists of 45 amino acids, comprised of 3 cysteine and 1 histidine residues ($CX_9CX_{10}CX_2H$; the C_3H) and rich in basic amino acids. The WRC domain is similar to the barley HRT (hordeum repressor of transcription), a zinc finger transcriptional repressor, which possesses a C_3H motif with identical spacing similar to GRF WRC (4) and has DNA-binding activity in barley, *Arabidopsis* and rice (14-16). Several studies revealed that all GRFs exhibit a putative NLS (Nuclear Localization Signal) due to their spacing pattern similarity with that of NLS. Several studies have revealed that all GRFs are confined to the nuclear region (4, 17, 18).

The TQL domain is present in the less conserved C-terminal region of the GRF protein, consisting of a stretch of 15 amino acid residues. The GGPL domain in the C-terminal region of GRF spans across 18 amino acid residues. The FFD domain in the C-terminal region of GRF consists of 19 amino acid residues (5, 19). The 3 domains that are present in the C-terminal region of the GRF protein are not present in all GRF members. The functions of these domains are not yet known. These C-terminal domains may not be present in all GRFs. In *Arabidopsis* and rice, the C-terminal region contributes to transactivation activity, as shown by the GAL4 yeast assay (8, 20). The TQL domain is present in *AtGRF1, 2, 3, 4 (Arabidopsis thaliana* GRF) and in *OsGRF1, 2, 3, 4, 5* while the GGPL domain is only found in *AtGRF1, 2, 3, 4* and in *AtGRF7* and *AtGRF8* as well as in *ZmGRF2, 8* and *13* (*Zea mays* GRF) but not in any of the 13 *OsGRFs*. The FFD domain is present in *ZmGRF1, 3, 5, 6, 7, 9* and *AtGRF4*. All 3 domains were absent in *ZmGRF4, 10* and *12* (21, 22).

Structure and function of GIF

GIF functions as a transcriptional co-activator by interacting with GRF. It exhibits similarity to the SNF (SYT (synovial sarcoma translocation) N-terminal homology) domain located in the N-terminal region of the SYT protein, which interacts with the QLQ domain of the human SWI/SNF complex. The SNF domain of GIF, also referred to as the SSXT (SSX (synovial sarcoma X breakpoint) -SYT translocation) domain, comprises 54 amino acid residues. The C-terminal region of GIF is enriched in glutamine and glycine residues, resembling the QPGY (glutamine-proline-glycine-tyrosine) domain of SYT, although it does not show strong sequence alignment with this domain. Due to its similarity with the human SYT domain, the GIF domain is believed to perform a comparable function. The SYT domain's ability to interact with the SWI/SNF complex's QLQ domain and serve as a transcriptional co-activator suggests that GIF and GRF, through their respective SNF and QLQ domains, form a functional interaction interface (20, 23). The molecular weight of the GIF protein ranges from 20 kDa to 25 kDa. *In vitro* and *in vivo* DNA binding studies show that the WRC domain initiates DNA binding (14, 15, 24). A recent study of structural and biochemical experiments of DNA binding activity shows GRF's DNA binding activity is stabilized by GIF; QLQ also interacts with the WRC domain, forming a self-inhibitory interaction for DNA binding activity when it binds to cis elements of the GRF family. When GIF interacts with QLQ, the inhibitory interaction is resolved, making the DNA site available for binding and enhancing stability (25). The total number of GIF copies in a species may vary from 1 to 8. One GIF gene was encountered in green algae. The GIF families have an ancient origin in green algae, as GIF was present in green algae, but not in GRF. As mentioned, GRFs are said to have evolved from charophyte algae. The green algae and charophyte algae belong to different clades. Normally, they both come under Viridiplantae, which includes both green algae and land plants. Viridiplantae is divided into two major lineages: 1) chlorophyta, which includes most of the green algae; 2) streptophyta, which includes charophytes and land plants. These charophytes are most closely related to land plants (26). It is said that GIF gene families might have evolved first than GRF TFs. The charophyte algae (*K. nitens*) have only one GIF gene (27). In angiosperms, *Arabidopsis*, rice and maize have 3 GIF copies; Wheat has 8 GIF copies (19, 22, 28, 29).

Diversity of *OsGRF* family

The phylogenetic tree was constructed based on GRF nucleotide sequences retrieved from NCBI (National Center for Biotechnology Information), GenBank repository. Comparative phylogenetic analysis revealed that the *OsGRF* family is organised into distinct clades with homologs from *AtGRF* (dicot) and *ZmGRF* (monocot) species, denoting conservation of core domains and evolutionary divergence from a common ancestor (Fig. 1). Three nodes were identified, resembling three clades. In this tree, Clade 1 includes *OsGRF2, 3, 4, 5* and *10*. Clade 2 comprises *OsGRF6, 7, 8* and *9*. Clade 3 consists of *OsGRF1, 11* and *12*. Most *OsGRFs* show strong topological association with monocot paralogs, indicating evolutionary relatedness. Notably, certain *OsGRFs* are grouped with *AtGRFs*, implying retention of certain ancestral characteristics even with monocot-dicot divergence. The GRF belonging to the same clade generally share conserved sequence motifs and possibly related biological

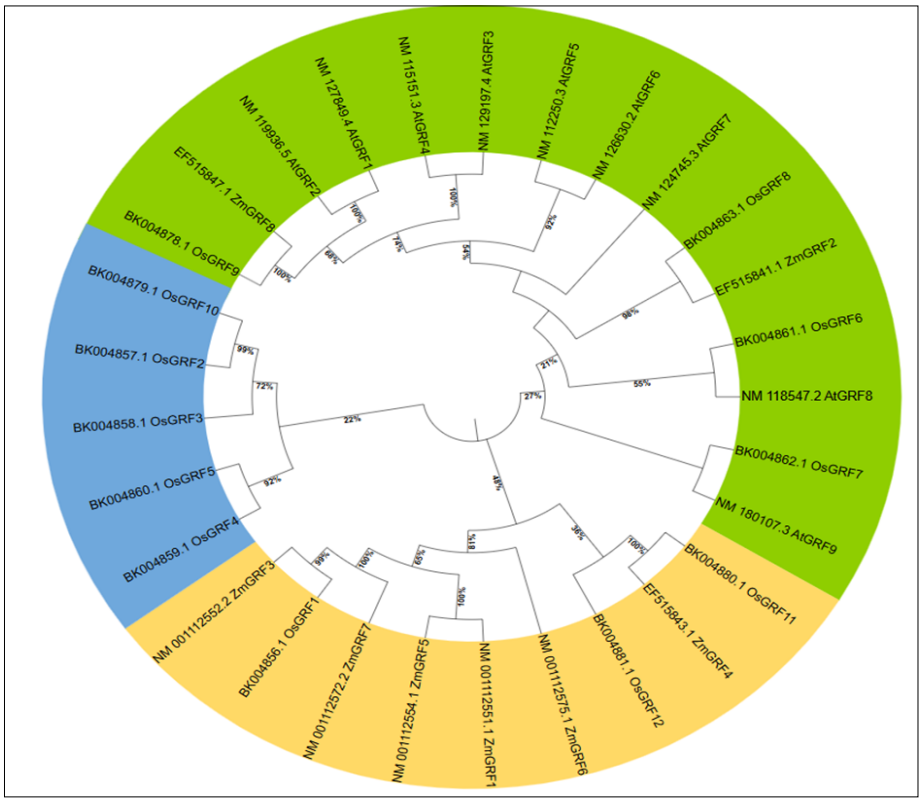

Fig. 1. Phylogenetic relationship among GRF proteins from *O. sativa* (*OsGRF*), *A. thaliana* (*AtGRF*) and *Z. mays* (*ZmGRF*). The tree with the maximum likelihood method based on 1000 bootstrap replicates using the MEGA11 software. Three phylogenetic clades of GRFs (A, B, C) were identified and are indicated in blue, green and mustard yellow, respectively.

functions but also have functional divergence due to gene duplication events. Therefore, experimental validation is required to confirm functional equivalence (Fig. 1).

GRF interaction with cis-acting elements in target gene promoters

The cis-regulatory element is present in the promoter region of the target gene, whose expression is regulated by particular transcription factors. The first GRF-regulated cis-element identified is TGTCAGG in the promoter of DREB2A (dehydration-responsive element binding protein 2A) in *Arabidopsis*, which represses osmotic stress-responsive genes under non-stress conditions (15). In rice, *OsGRF6* and *OsGRF10* bind to TGTGTTG (GA responsive element) of *OsJMJ706* (JMJD2 family jmjC gene 706) and *OsCR4* (crinkly 4 receptor-like kinase) promoter regions, leading to increased expression of these genes, which results in floret development (24). *OsGRF6* binds to the CGSMR of *ARF2*, *ARF7* (auxin response factor) promoter region, resulting in the upregulation of *OsGRF6*, which in turn promotes the auxin signaling pathway and inflorescence development (30). Phylogenetic analyses revealed that GRF and GIF genes have cis-acting elements in their promoter region and co-evolved over time. Light-responsive elements, hormone and stress-responsive elements are found in the cis-acting elements. These elements can induce GRF expression in many plant species (13, 27). A study on cis-acting elements was carried out in gramineae crops, including rice, maize, sorghum and barley, indicating that 41 types of cis-acting elements are unevenly distributed in the GRF promoter region. Among them, 18 types of cis-acting elements were related to growth and development (9).

miRNA-mediated expression of GRF

Post-transcriptionally, the gene expression is regulated by small RNAs such as miRNA (micro RNA) and siRNA (small interfering RNA) in plants (31). miRNAs are a small group of non-coding regulatory RNAs that consist of 21 to 24 nucleotides (32). The mature miRNA is processed from endogenous miRNA in the nucleus to pri-miRNA (primary miRNA), which has a specialized stem loop structure and is transcribed by RNA polymerase II and III. Pri-miRNA is then converted to mature miRNA with the help of DCL (dicer-like) enzymes (32), further processed into a miRNA-miRNA duplex and its 3' end is methylated by the HEN1 (Hua enhancer 1) enzyme (33) before being transported to the cytoplasm. Then it recruits RISC (RNA-induced silencing complex) along with AGO (argonaute) proteins that bind to the complementary region of target mRNA, which either leads to mRNA degradation or translational repression (34). Some miRNAs are conserved, which have identical target sites in some species; sometimes conserved miRNAs may bind to non-identical targets (35). *miR396* is one of the conserved plant miRNA genes that specifically target GRF mRNA transcripts. When miRNA binds to the miRNA recognition sequence of the GRF gene, the expression pattern of the GRF gene is downregulated. When a plant encounters stress, the miRNA accumulates, leading to lower expression of GRF (Fig. 2) (36). This is a strategy to conserve energy under stress by reducing growth activities (37). In rice, there are a total of 160 miRNA target genes have been identified. Among them, 56 targets were specific to 29 rice-specific miRNAs (38). *miR396* has 11 conserved target GRF sites except for *OsGRF11*, as mentioned in the Table 1 (39-42, 43). In rice, the *miR396* family includes variants as *miR396a-miR396i* (44). *miR396d* differed from *miR396a, b* and *c* by 3 nucleotide differences and is found only in monocots (45). There are abundant variants in monocots like rice, maize and purple false brome and the variant which was first detected in rice was the insertion of 'G' at the 7th-8th position of miRNA (46). This variation may have different effects biochemically and at the gene regulation level (47-49).

Table 1. GRF members in rice, their chromosomal location, response to miRNA regulation, expression pattern and GRF genes' sensitivity to hormonal response

S. No.	GRF	Chromosome no.	Gene Id	miRNA regulation	Expression pattern	Hormonal response	References
1	*OsGRF1*	2	Os02g0678800	*miR396*	Young leaves, leaf primordia, shoot apical meristem and grain	GA and ABA sensitive	(29)
2	*OsGRF2*	6	Os02g0701300	*miR396*	Leaf primordia and culm	BR sensitive	(8, 39)
3	*OsGRF3*	4	Os02g0776900	*miR396*	Young inflorescence	GA sensitive	(8, 16)
4	*OsGRF4*	2	Os03g0674700	*miR396*	Young panicles and separated grain husk	BR, cytokinin and strigolactone sensitive	(40, 41)
5	*OsGRF5*	6	Os03g0729500	*miR396*	Developing leaves, young panicles and actively growing tissues	Unknown	(8)
6	*OsGRF6*	3	Os04g0574500	*miR396*	Young inflorescence	GA, BR and IAA sensitive	(24)
7	*OsGRF7*	12	Os04g0600900	*miR396*	Axillary buds, lamina joints, nodes, internodes and young inflorescence	GA sensitive	(42)
8	*OsGRF8*	11	Os06g0116200	*miR396*	Young leaves, nodes and internodes	GA sensitive	(42)
9	*OsGRF9*	3	Os07g0467500	*miR396*	Panicle meristem, young inflorescence and young leaves	GA sensitive	(8)
10	*OsGRF10*	2	Os11g0551900	*miR396*	Young inflorescence	GA sensitive	(24)
11	*OsGRF11*	7	Os12g0484900	Nil	Young inflorescence	Unknown	(8, 24)
12	*OsGRF12*	4	Os06g0204800	*miR396*	Stem, shoot	GA sensitive	(8)

OsGRF: *O. sativa* growth regulating factor, miR396: microRNA396, GA: Gibberellic acid, ABA: Abscisic acid, BR: Brassinosteroid, IAA: Indole acetic acid

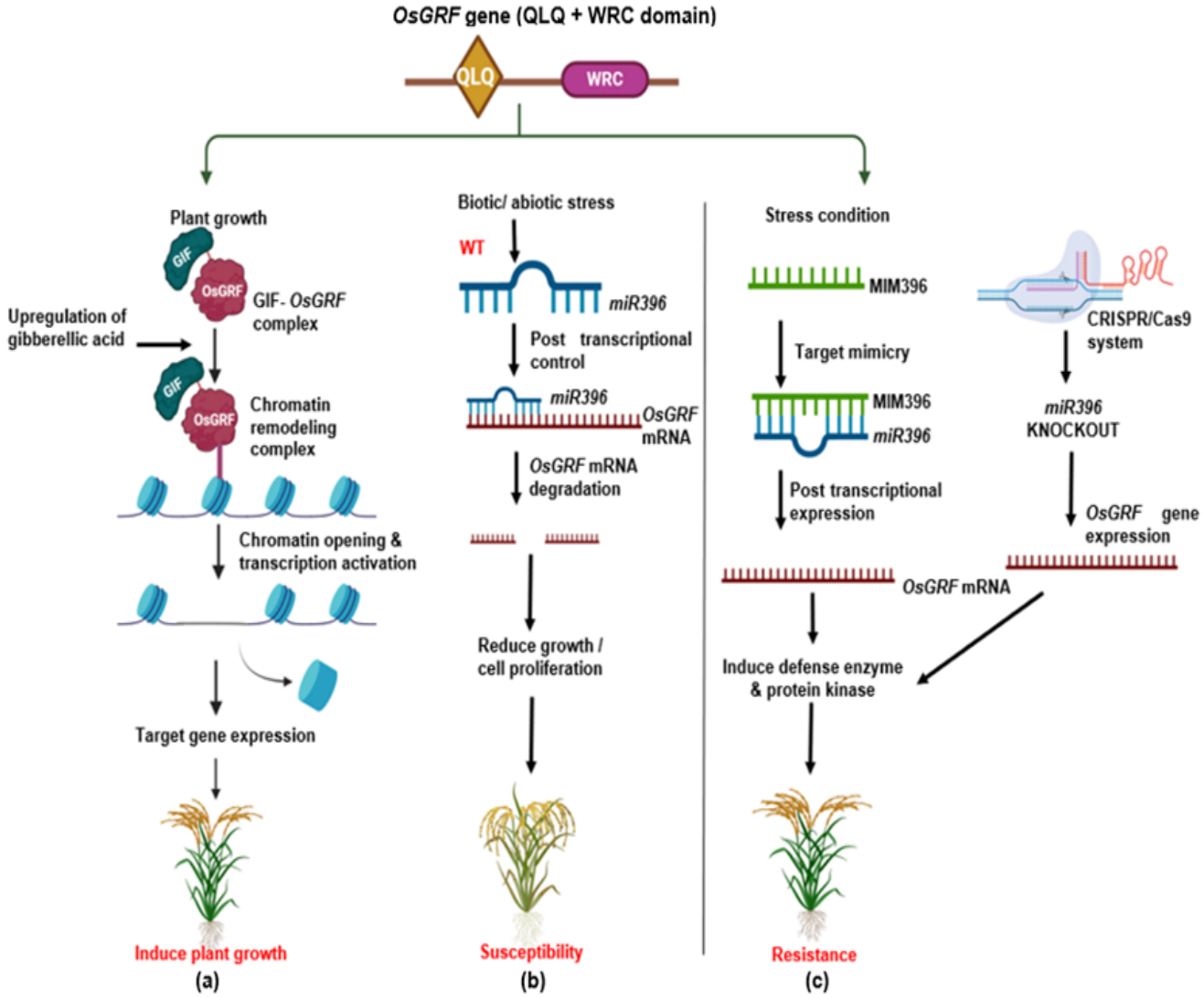

Fig. 2. Schematic representation of GRF TF gene regulation: (a) under normal conditions; (b) during stress, where miR396 binds to the recognition sequence of OsGRF mRNA, reducing growth; (c) during stress with MIM396 (target mimic of miR396) or CRISPR/Cas9 restricting miR396 binding, thereby promoting defense mechanisms.

OsGRF: *O. sativa* growth regulating factor, QLQ: Glutamine-leucine-glutamine, WRC: WRKY rich cysteine, GIF: GRF interacting factor, WT: Wild type, *miR396*: microRNA396, mRNA: messenger RNA, MIM396: Mimicry of miR396, CRISPR/Cas9: Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein 9.

Functions of *OsGRFs*

The expression of the *OsGRFs* is tissue-specific and constitutive, as its expression is found in all tissues. The GRF, QLQ domain interacts with the SNF domain of GIF and targets the downstream gene. This complex removes the nucleosome and allows the complex to interact with the gene, which leads to upregulation of target gene expression that regulates plant growth (Fig. 2). For GRF -GIF interaction, GIF is one of the important regulators for the expression of GRF. Since knockdown of GIF genes by RNAi in rice shows shorter stems, shrunken leaves, withered seeds, less number of roots with slenderness, while overexpression of GIF genes shows no phenotype difference (17). This shows that GIF was expressed ubiquitously in all tissues and the GRF-GIF duo is essential for plant growth and defense mechanisms. Through CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein 9) technology and target mimicry of *miR396* (Fig. 2), the GRF expression is increased, which improves plant development, floral organogenesis, increases grain size and defence mechanisms against biotic and abiotic stresses (Fig. 3), which are discussed below.

Role in rice leaves

The tissue-specific expression analysis, conducted through qRT-PCR, reveals that *OsGRF1, 2, 5, 7, 8, 9* and *12* are expressed in leaves. The first GRF identified, viz., *OsGRF1*, is induced by gibberellic acid (GA). Initially, it was found to be involved in stem elongation; later, it was found to be associated with leaf development (4). miRNA negatively regulates *OsGRF* expression. The binding of miRNA to the *OsGRF* transcript reduces the expression of GRF genes. *OsGRF1* and *OsGRF2* are involved in leaf development. Double mutants of *OsGRF1* and *OsGRF2* have increased leaf angle, narrow leaves and twisted flag leaf due to abnormal vascular bundle development. This double mutant downregulated *DL* (drooping leaf), which functions in midrib formation and upregulated *BR* (Brassinosteroid) related genes. The miRNA-resistant mutant line showed reduced leaf angle, erect leaves and upregulated the *DL* gene. The *OsGRF1* and *2* negatively regulate leaf angle (39). Overexpression of mutants of *OsGRF1* and *2* together resulted in lowered leaf angle. Lowered leaf angle in high-density planting, like rice, has more light penetration, increased photosynthetic efficiency and improved air flow (50).

By comparing overexpressing lines of *OsGRF1* and miRNA-resistant lines of overexpressing *OsGRF1* with those of the wild type, the mutated miRNA-resistant line showed tongue-like shaped leaves with a stalk, while wild type and overexpressing lines of *OsGRF1* showed incomplete, needle-like leaves in the seedling stage. Knockdown of *OsGRF1* through RNA interference resulted in shrunken leaves. The increase in leaf size in the miRNA-resistant line is due to increased cell proliferation. The cell-cycle-related genes *cycOs1* and *cycOs2* (cyclin *O. sativa* 1 and 2) were also upregulated in the miRNA-resistant line and downregulated in knockout lines. This indicates that *OsGRF* might regulate cell cycle-related genes (29). *OsGRF1* plays an important role in controlling the heading (flowering) date in rice. In the *rhd1* (reduced heading date) mutant lines, downregulation of *OsGRF1* leads to an earlier heading date by approximately 20 days. Conversely, transgenic lines with suppressed expression of *OsGRF1* exhibit delayed heading. This variation in heading time is attributed to the tissue-specific and developmentally regulated expression pattern of *OsGRF1* (51). *OsGRF7* and *OsGRF8* regulate leaf development in rice. A gene silencing experiment, along with GA treatment and transcriptome profiling, reveals that they show lower expression and reduced leaf size (42).

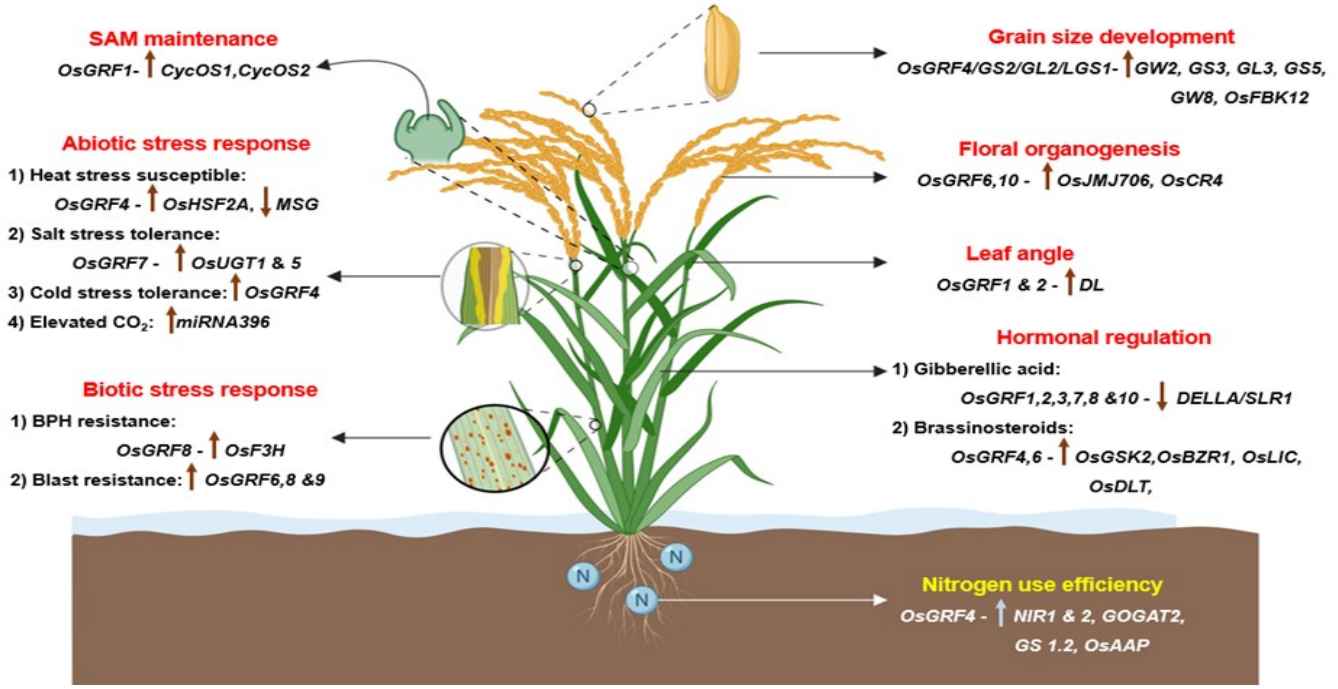

Fig. 3. GRF family members play various roles throughout plant growth and development. The upward arrow indicates upregulation of genes and the downward arrow indicates downregulation of genes under OsGRF expression.

OsGRF: *O. sativa* growth regulating factor, SAM: Shoot apical meristem, *CycOs*: Cyclin *O. sativa*, *HSF*: Heat shock factor, *MSG*: Male sterile gene, *UGT*: Uridine diphosphate glycosyltransferase, *miRNA396*: micro RNA396, *F3H*: Flavanone 3-hydroxylase, *GS*: Grain size, *GL*: Grain length, *LGS*: Long grain size, *GW*: Grain width, *FBK*: F-box and Kelch domain, *JMJ*: JMJD2 family jmjC, *CR4*: Crinkly 4 receptor-like kinase, *DL*: Drooping leaf, *DELLA/SLR1*: DELLA protein/Slender Rice1, *GSK2*: Glycogen synthase kinase-3 (GSK3)-like kinase 2, *BZR1*: Brassinazole-resistant 1, *LIC*: Leaf and tiller angle increased controller, *DLT*: Dwarf and low-tillering, *NIR*: Nitrite reductase, *GOGAT2*: Glutamine: 2-oxoglutarate aminotransferase, *GS*: Glutamine synthetase, *AAP*: Amino acid permease.

Role in floral organogenesis

OsGRF6 and *OsGRF10* are involved in floral organ development mediated by *OsmiR396d*. *OsGRF6* and *OsGRF10* bind to the GA-responsive element present in the upstream promoter region of the JMJD2 family jmjC gene 706 (*OsJMJ706*) and the crinkly4 receptor-like kinase (*OsCR4*). *OsJMJ706* encodes H3K9 demethylase, whose function is to regulate floral organ development and *OsCR4*, whose function is to regulate the interlocking of palea and lemma by epidermal cell differentiation (52, 53). These GRFs interact with *OsGIF1* and bind to the promoter elements of the *OsJMJ706* and *OsCR4* and upregulate *OsJMJ706* and *OsCR4* genes. These genes regulate husk opening and floral organ identity. The single mutants of these GRFs show a semidwarf phenotype with no difference in floret development, while double mutants of *OsGRF6*/*OsGRF10* show long sterile lemma, missing palea and an abnormal number of stamens. So, both GRFs act redundantly in rice floral development. The miRNA-resistant line, antisense transgenic lines and double mutants showed abnormal floret phenotype and the overexpressing lines rescued the abnormal phenotype and resulted in normal floret development (24).

Role in grain size

OsGRF4 encodes *GS2* (grain size on chromosome 2), a QTL that regulates grain size in rice mediated by *miR396c*. *OsGRF4* enhances grain length, width and thickness, resulting in higher 1000-grain weight and overall grain yield. A mutation created in the miRNA binding region leads to overexpression of *OsGRF4*, resulting in increased grain size (40). This effect is due to the cell proliferation and cell expansion of epidermal cells of grains. Further analysis revealed that other grain size regulating genes, *GW2, GS3, GL3, GS5, GW8, OsFBK12* and *GIF1* were also overexpressed in *GRF4* overexpressing plants. Cell cycle related genes, *E2F2, CYCA2.1, CYCA2.2, CYCA2.3, CDKA2, CDKB* and *CYCT1* were also upregulated (54). Therefore, *OsGRF4* regulates the other grain size-regulating genes and cell cycle-related genes, resulting in an overall increase in grain size. *OsGRF4* also regulates panicle length, seed shattering, cold stress response, carbon and nitrogen use efficiency (55-57). The *GL2* gene also encodes *GRF4*, which regulates grain size in rice mediated by *OsGIF* interaction along with brassinosteroid-responsive gene (41).

Hormonal regulation of OsGRFs

GA induces the expression of *OsGRFs*, while the expression is reduced when the 2-week-old seedling of rice is subjected to biotic and abiotic stresses like salt, drought, UV (Ultra-Violet), pathogen and ABA (abscisic acid). The expression pattern is less when they are exposed to such stresses, particularly under ABA stress. This strategy reduces the energy consumption required for GRF during stress conditions (29). External application of GA3 increased the expression level of *OsGRF7* and *OsGRF8*, which in turn increased the cell cycle-related genes *OsCYCB1;4* and *OsCYCA3;2*, resulting in increased leaf size in rice (42). GA signalling is mediated by the DELLA protein/*GID1* (gibberellin-insensitive dwarf1). When a plant is under stress conditions, the GA level would be low, the DELLA protein/*SLR1* (slender rice1) binds to *OsIDD2* (indeterminate domain 2), which in turn binds to the promoter of *OsmiR396*. This led to decreased expression of *OsGRF,* resulting in a dwarf phenotype. In the presence of GA, the DELLA protein is degraded, so the *miR396* level is lower, which increases the GRF expression (37). Rice *GL2*/*OsGRF4* gene is mediated by the brassinosteroid response gene *GSK2* (glycogen synthase kinase-3 (GSK3)-like kinase 2), which negatively regulates the *GL2*/*OsGRF4* gene by reducing the grain size (41). Cytokinin (isopentenyladenine riboside, trans-zeatin-riboside, cis-zeatin and cis-zeatin-riboside) and cytokinin-related genes (*CKX5* and *CKX1*) were upregulated in overexpressing lines of *OsGRF4*, resulting in increased grain size, panicle length and control seed shattering (55). *OsmiR396d*, regulated by *OsBZR1* (Brassinazole-Resistant 1), suppresses *OsGRF4* expression, resulting in increased leaf angle and also negatively regulates GA signalling and GA biosynthesis and reduces *OsGRF6* expression, which results in semi dwarf phenotype, thereby regulating plant architecture (58).

Role in nitrogen use efficiency

Under a low level of nitrogen supply, plants accumulate strigolactones, which degrade the dwarf 53 (*D53*) gene and DELLA/*SLR*, causing *OsGRF4* to bind to its target site and regulate nitrogen-responsive genes. Plants adapt to low N conditions through seminal root growth, irrespective of nitrogen supply (developmental adaptation) and reduced N translocation by reducing *GS1* (glutamine synthase) expression (metabolic adaptation) (59). *OsGRF4* promotes nitrogen assimilation, carbon metabolism and nitrogen use efficiency, while DELLA proteins act opposite to *OsGRF4,* have low nitrogen use efficiency and a dwarf phenotype, which is employed in green revolution varieties. To develop a semi-dwarf variety with NUE is important for future cultivation practices. Balancing *OsGRF4* and DELLA can improve yield and productivity (57). Nitrogen assimilation genes (*NIR1, NIR2, GOGAT2, GS1.2* and *OsAAPs*) were upregulated in *miR396e* and *miR396f* mutants, enhancing *OsGRF4, OsGRF6* and *OsGRF8* expression even under N-deficient conditions (60).

Role in biotic stresses

OsGRFs expression can provide resistance to biotic stress, such as insects and pathogens. *OsGRF8* showed resistance to BPH (brown plant hopper). *OsmiR396a* and *b* regulate the *OsGRF8* expression; the target mimicry of miRNA target site leads to increased expression of *OsGRF8*, which, in turn, the GRF binds to the promoter region of flavonoid biosynthesis gene *OsF3H* (flavanone 3-hydroxylase). F3H is one of the important components in secondary metabolites production that protect plants against stress conditions. Flavonoids protect plants against environmental and biotic stresses. Flavonoids are good antioxidants that scavenge reactive oxygen species (61) and also deter feeding and avoid oviposition of insects (62). These sequestered *miR396* lines showed increased resistance to BPH and salicylic acid signalling pathway genes might act along with it. They exhibit an antibiosis strategy by which they reduce the insect survival rate or feeding rate. The resistant plants also showed longer grains and improved seed quality (63). *OsGRF6*, *7, 8* and *9* are involved in rice blast disease resistance caused by the fungus *Magnaporthe oryzae*. The overexpressing lines of *OsGRF6, 7, 8* and *9* showed fewer lesions and minimal appressorial growth. These GRFs are regulated by *miR396*. These overexpression lines are resistant to the disease. However, only *OsGRF6, 8* and *9* showed better resistance without compromising the yield. The *OsGRF7* showed resistance, but also had yield defects (64).

Role in abiotic stresses

OsGRFs regulate plant growth and development by protecting plants under stress conditions. Several *OsGRFs* were found to be involved in abiotic stresses such as salt stress, heat stress, cold stress and elevated CO_2 conditions. *OsGRF4* regulates plant

growth under cold stress and heat stress. Under cold stress, the seedlings were grown under 4 °C, the expression levels of *OsmiR396* increased concurrently with decreased *OsGRF4* activity. After transfer from cold stress to normal conditions, the *OsGRF4* expression increased with higher seedling recovery (56). This *OsGRF4* is susceptible to heat stress, especially during pollen development. Heat stress is one of the major limiting factors for pollen development (65, 66). When *GS2* containing the *GRF4* allele is subjected to heat stress, the pollen viability and pollen development are reduced. This may be due to the downregulation of transcription factors regulating pollen development and the downregulation of genes regulating photosynthesis and chlorophyll development, which are needed for pollen nutrients. Alternate splicing of *OsGRF4* gene could be a part in creating pollen vulnerability. The pollen vulnerability could be caused by heat stress or due to an alternate splicing event in the *GS2* line (67). Plants use proline, malonaldehyde, soluble sugars, chlorophyll content and reactive oxygen species (ROS) as markers when they are under stress (68). *OsGRF7* regulates salt stress in rice by being involved in arbutin biosynthesis. Arbutin has antioxidative activity through the hydroquinone moiety, which suppresses the accumulation of ROS and protects the lipid membrane integrity (69). The overexpressing lines of *OsGRF7* under salt stress conditions showed increased expression of arbutin biosynthesis genes *OsUGT1* and *OsUGT5* (uridine diphosphate glycosyltransferase), which confer resistance to salt stress and increased grain size. *OsGRF7* is degraded by *OsFBO13* (rice F-Box O13), which negatively regulates *OsGRF7* against salt stress (70). Under elevated CO_2 conditions, *miR396e* and *miR396f* showed higher expression thereby regulating lower expression of *OsGRF3, 6* and *10* resulting in leaf blade size reduction, in turn reduces the photosynthetic rate. This phenotype could be acclimated to increasing CO_2 conditions in the future (71).

Conclusion

As a significant staple crop that is relied upon by half of the world's population, a deeper comprehension of the GRFs in rice contributes significantly to enhancing productivity. The study of GRFs' function in growth development, grain yield and defense mechanisms paves the way to regulate genes responsible for targeted traits. CRISPR/Cas9 technology, target mimicry of microRNA strategy, RNAi and antisense strategies have been employed to overexpress GRF genes by suppressing miRNA activity. Similarly, overexpressing specific miRNAs has been used to study gene function and regulation. Although the molecular mechanisms underlying GRF transcription factors remain partially unclear, it is evident that they regulate downstream genes involved in growth, development and defence mechanisms. Several evolutionary studies have been carried out for a better understanding of the gene. Overexpressed GRF lines developed through transgenic approaches can be incorporated into breeding programs to enhance grain size, improve plant architecture and increase grain yield and production. Conversely, suppressing the expression of certain GRFs can produce semi-dwarf varieties, a key trait that contributed to the success of Green Revolution crops. Engineering-specific GRF expression by targeting related miRNA can be designed to achieve precise desired traits.

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Authors' contributions

RM, RV, KE, VS, MV and UM conceived and designed the manuscript. RM compiled the material and wrote the manuscript. RV designed the figures. KE reviewed the manuscript. RM did the final editing and KE approved the final draft. All authors read and approved the final manuscript.

Compliance with ethical standards

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