

## REVIEW ARTICLE

# The Journey from Two-Step to Multi-Step Phosphorelay Signaling Systems

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**Abstract: Background:** The two-component signaling (TCS) system is an important signal transduction machinery in prokaryotes and eukaryotes, excluding animals, that uses a protein phosphorylation mechanism for signal transmission.

**Conclusion:** Prokaryotes have a primitive type of TCS machinery, which mainly comprises a membrane-bound sensory histidine kinase (HK) and its cognate cytoplasmic response regulator (RR). Hence, it is sometimes referred to as two-step phosphorelay (TSP). Eukaryotes have more sophisticated signaling machinery, with an extra component - a histidine-containing phosphotransfer (HP-T) protein that shuttles between HK and RR to communicate signal baggage. As a result, the TSP has evolved from a two-step phosphorelay (His-Asp) in simple prokaryotes to a multi-step phosphorelay (MSP) cascade (His-Asp-His-Asp) in complex eukaryotic organisms, such as plants, to mediate the signaling network. This molecular evolution is also reflected in the form of considerable structural modifications in the domain architecture of the individual components of the TCS system. In this review, we present TCS system's evolutionary journey from the primitive TSP to advanced MSP type across the genera. This information will be highly useful in designing the future strategies of crop improvement based on the individual members of the TCS machinery.

## ARTICLE HISTORY

Received: September 16, 2020  
Revised: November 21, 2020  
Accepted: December 18, 2020

DOI:  
10.2174/1389202921666210105154808

**Keywords:** Two-component system, histidine kinases, histidine-containing phosphotransfer proteins, response regulators, multi-step phosphorelay, two-step phosphorelay.

## 1. INTRODUCTION

Environmental stresses in the form of biotic and abiotic factors constitute a significant threat to plants. Among the higher plants, crop plants are more sensitive to abiotic stresses as they pay a heavy toll in the form of yield losses [1]. Yield declines upto 50–70% in cereals, such as rice, wheat, and maize have been reported, due to salinity, drought, and extremes of temperature [2, 3]. Plants have developed complex signal transduction mechanisms to recognize various stresses to ensure their survival and development under unfavorable conditions [4].

Climate-smart agriculture is envisioned to ensure food security for the growing population. Furthermore, for raising climate-smart crops, it is necessary to understand the signaling machinery playing a significant role in crop adaptation to aforesaid environmental stresses. Protein phosphorylation is a commonly conserved post-translational modification re-

gulating cellular activities in many signaling pathways. Phosphorylation occurs at the specific amino acid residues, such as serine (Ser), threonine (Thr), tyrosine (Tyr), and histidine (His) [5]. While Ser, Thr, and Tyr kinases are prevalent in both prokaryotes and eukaryotes, His kinases (HK) were initially thought to be restricted only to prokaryotes [6]. However, later studies confirmed their presence and involvement in eukaryotes, excluding animals [7-9]. The two-component signaling (TCS) system is an ancient conserved signaling machinery based on HK phosphorylation, translating the signal from the environment to the downstream members [10, 6]. TCS is widely distributed from lower organisms (*e.g.*, bacteria) to higher eukaryotes (*e.g.*, plants) but is absent in metazoa [11]. Numerous studies have shown that TCS members play a significant role in diverse bioprocesses, such as abiotic stress signaling, hormone signaling, chemotaxis, nitrogen metabolism, biotic stress signaling, quorum sensing, and plant growth and development [12-15].

The expression of various TCS genes is modulated by different environmental stresses [16, 17]. Thus, TCS gene members may act as potential candidates for the generation of stress-tolerant transgenic crops. To fully understand the molecular mechanism behind plant stress tolerance, it is ne-

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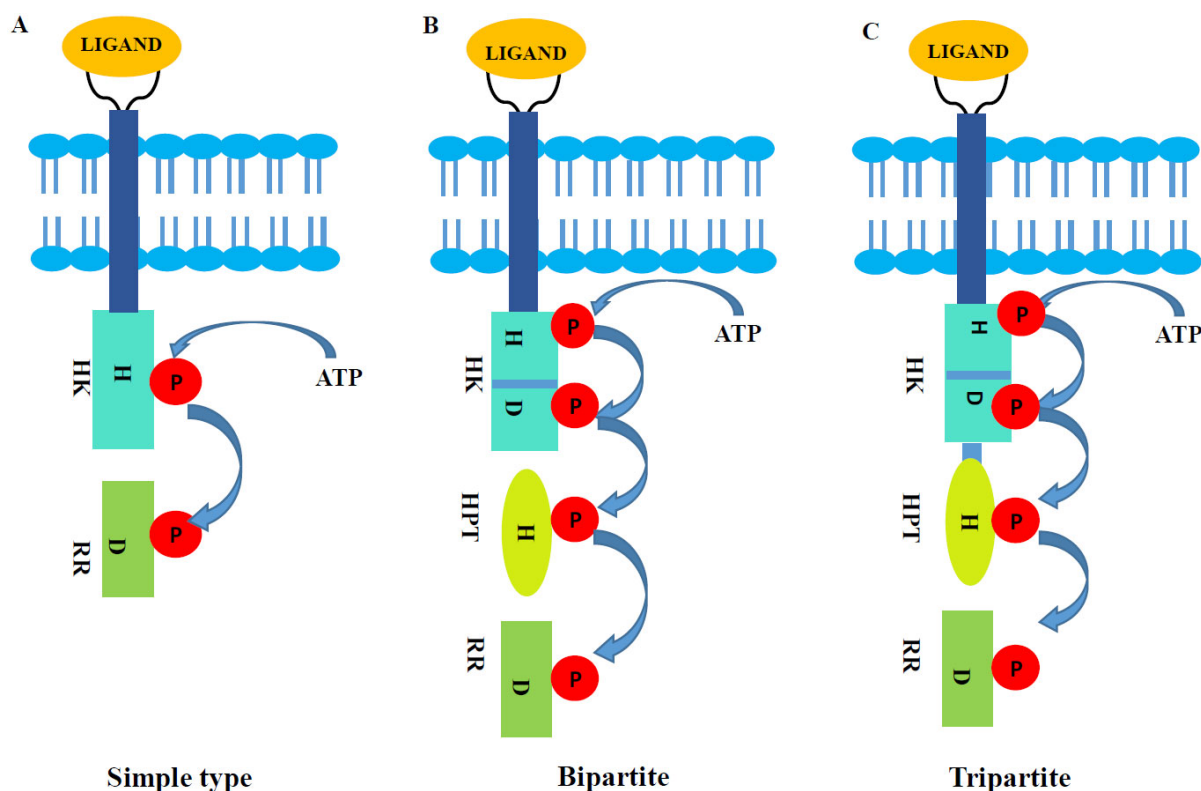
necessary to understand the cascade mediators and their role in the transduction pathway. In the present work, we have carried out detailed investigations towards charting out the evolutionary trajectory of key domains of TCS gene members across the genera. Our analysis reveals how signaling migrates from two-step signaling partners towards a multi-step signaling network for fulfilling the needs of the changing environment with rising structural complexity in the diverse organisms.

## 2. OVERVIEW OF TCS SYSTEM

### 2.1. Canonical TCS System

The canonical TCS system, also known as simple or prototypical TCS, is the most primitive signaling; The two lines should be connected and can be reframed as- it was discovered in *E. coli* e.g., EnvZ-OmpR sensing system [18]. Canon-

ical TCS signaling is typically characterized by the involvement of two components: membrane-bound HK and a cytosolic response regulator (RR). Histidine kinases are the primary sensing unit that senses the signal and transmits it to downstream members for further response. It generally acts as a protein dimer and contains an extracellular sensor domain and intracellular kinase domain with a conserved His residue. The RR carries an aspartate (Asp)-containing receiver module and an effector domain. Upon receiving the signal from the external environment, the His residue of HK is autophosphorylated. The cascade involves the transfer of the phosphoryl group from this His residue of HK to the conserved Asp residue of RR (Fig. 1A). The prototypical TCS is prevalent in prokaryotes only. The EnvZ-OmpR osmosystem in *E. coli* is a well-characterized, canonical TCS that is mainly involved in osmosensing [18]. The NtrB-NtrC osmosystem in *E. coli* involved in nitrogen metabolism is another example of canonical TCS.



**Fig. (1).** Two-component signaling system (TCS) (A) Simple type TCS. Upon receiving the signal, the histidine kinase (HK) is autophosphorylated at a conserved histidine (His) residue in the transmitter domain, and the phosphoryl group is then transferred to a conserved Asp residue in the receiver domain of a response regulator (RR). (B) Bipartite type TCS. Bipartite TCS includes hybrid histidine kinase (HHK) that is autophosphorylated at a conserved His residue in its transmitter domain, and the phosphoryl group is then transferred to a conserved Asp residue in the receiver domain of the HHK. The high energy phosphoryl group is then transferred to a conserved His residue in Hpt and finally to a conserved Asp residue of the RR. (C) Tripartite type TCS. Tripartite TCS includes HHK that is autophosphorylated at a conserved His residue in its transmitter domain, and the phosphoryl group is then transferred to a conserved Asp residue in the receiver domain of the HHK. The phosphoryl group is then transferred to a conserved His residue in the Hpt domain present within the HHK and finally to a conserved Asp residue in the receiver domain of RR. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

## 2.2. Multi-step TCS System

The multi-step TCS system has been reported in eukaryotes and is involved in various facets such as photoreception, osmosensing, hormone signaling, circadian rhythm regulation, and different biotic and abiotic stress responses [19-22]. The multi-step TCS system includes an additional Asp-containing receiver domain in the HK protein, referred to as hybrid histidine kinase (HHK), and a histidine-containing phosphotransfer protein (Hpt), which acts as a mediator of the phosphorelay between HK and RR. Hybrid TCS is more dominant in eukaryotes but is also present in some prokaryotes, *e.g.*, plant cytokinin receptor kinase (PcrK) in *Xanthomonas campestris* [23]. Upon receiving the signal, HHK autophosphorylates in the conserved histidine residue, and the phosphate is passed to the conserved Asp residue of the receiver domain of HK, followed by the His residue of Hpt protein, and ultimately the Asp residue of RR. The Hpt can be present as a domain in HK or as a separate protein that can shuttle between HK and RR; thus, HHKs can be tripartite and bipartite, respectively (Fig. 1B and 1C). Bipartite HHKs are mostly present in eukaryotes, while tripartite HHKs are prevalent in prokaryotes.

TCS systems evolved from a two-step phosphorylation pathway to a multi-step phosphorylation pathway through the incorporation of various domains and proteins. The journey of TCS from prokaryotes to eukaryotes includes multiple phenomena, such as gene duplication, mutation, gene fusion/fission, domain shuffling, lateral gene transfer, and the involvement of additional proteins [24-26]. The number of TCS genes in an organism depends on the nature of their ecological habitat, *e.g.*, organisms living in continuously varying environmental conditions need more genes to regulate their system. For a holistic view of TCS systems, we investigated the phylogenetic information and the domain architecture of TCS in different organisms.

## 3. FROM TWO-STEP PHOSPHORELAY TO MULTI-STEP PHOSPHORELAY

Two-step phosphorylation regulates various processes in prokaryotic machinery and involves three phosphotransfer reactions (i) autophosphorylation of HK at conserved His residue, (ii) phosphorylation of RR at the conserved Asp residue, and (iii) dephosphorylation of RRs. The two-step phosphorelay signaling evolves to multi-step phosphorelay (MSP) signaling as the organism's habitat and cellular complexity change. The MSP might enable the necessary adaptations for survival in the changing environment. It involves hybrid HKs with an extended C-terminal domain, known as the receiver domain, which contains a conserved Asp residue and additional phosphor intermediate proteins known as His-containing phosphotransfer proteins (Hpts). This shuttle protein moves continuously between cytoplasm and nucleus, and on phosphorylation, activates RRs by transferring the phosphoryl group to the conserved Asp residue of RR [27].

Most HKs in eukaryotes are the hybrid type and involve five phosphotransfer reactions (i) autophosphorylation of HK at conserved His residue, (ii) phosphotransfer from His

to an Asp of HK, (iii) phosphorylation of Hpt at the conserved His residue, (iv) phosphorylation of RR at the conserved Asp residue, and (v) dephosphorylation of RRs. Higher eukaryotes have the most advanced multi-step phosphorelay system, which evolved from early-diverging land plants, such as algae, mosses, and bryophytes [28]. The Hpt domain, which provides conserved His residue in some prokaryotes, such as CheA where the kinase domain lack conserved His residue, evolved as an individual mediator protein for connecting HK to RR in higher organisms [29, 30].

## 4. TCS MACHINERY IN DIFFERENT DOMAINS OF LIFE

### 4.1. Prokaryotic Two-component System

Most prokaryotes use the simple type of TCS machinery to regulate their processes. In prokaryotes, such as archaea and eubacteria, TCS plays a vital role in their responses to environmental cues, nutrient sensing, motility, sporulation, secondary metabolite production, and virulence [31-35], and is also involved in nitrogen, glucose, and cell wall biosynthesis [36, 37]. To fully understand the evolution of the TCS system, we investigated the overall domain architecture of TCS members in different kingdoms.

#### 4.1.1. Bacteria

In bacteria, the TCS system is of the simple type. In *E. coli*, EnvZ–OmpR is for the osmotic stress response, CheA–CheY regulates bacterial motility in response to chemotaxis, PhoR–PhoB is involved in phosphate regulon gene expression, and NtrB–NtrC is for regulating nitrogen metabolism [18, 38, 39]. The MtrB–MtrA TCS cascade in *Corynebacterium glutamicum* regulates the osmotic stress response and cell wall metabolism. The first HHK to be discovered in prokaryotes was *E. coli* BarA, which is involved in carbon metabolism [40-42], followed by *E. coli* ArcB [42]. The CheA protein of *E. coli* lacks conserved His residue in the H-box and uses the His-containing phosphotransfer (HPT) domain to transfer the phosphoryl group to the downstream RR (CheY), while the H-box was used for dimerization [43]. Additional domains such as HAMP and PAS are involved in phosphorylation and stimulus sensing, respectively. Phytopathogenic bacteria mostly have a hybrid type of HK as they use plant hormones to evade their host system [22]. Thus, they develop machinery to use plant metabolites and hormones as fuel for their survival. For example, *Sinorhizobium meliloti* HK Mt CRE1 and RRs Mt RR1 and Mt RR4 are involved in the crosstalk between the symbiotic bacteria and host plant to regulate nodule formation [44]. Hence, the identification of HHKs in prokaryotes, especially symbiotic bacteria, indicates that as the niche becomes more complex, new genes evolve and signaling occurs.

#### 4.1.2. Archaea

Archaeobacteria are inhabitants of harsh environments and thus adapt to tolerate extreme conditions. TCS is less

prominent in archaea but is involved in the essential processes, such as chemotaxis and phototaxis [45-48]. Archaea acquired the TCS system from bacteria through horizontal gene transfer [49, 50]. Many TCS members have been identified in Euryarchaeota and Thaumarchaeota [51]. Typical archaeal HKs are characterized by the presence of cytoplasmic PAS and GAF (cGMP-specific phosphodiesterases-adenylyl cyclases-FhlA) domains [52]. Other HKs may contain sensor domains, such as MEDS and PocR [53, 54]. The LtrK-LtrR TCS system of an Antarctica methanogen, *Methanococcoides burtonii*, regulates the activities of many temperature-dependent genes [55]. The RR LtrR has REC and Helix Turn Helix (HTH) domains. Li *et al.* [56] reported that chemotaxis in *Halobacterium salinarum* is regulated by HK CheA and RRs CheY and CheB. The FilI-FilR1 and FilR2 TCS systems regulate many methanogenesis genes in *Methanosaeta harundinacea* [56]. FilR1 includes the receiver domain and the HTH domain, while FilR2 contains only the receiver module. The number of TCS members varies among different archaeal species. In *Methanobacterium thermoautotrophicum*, there are 16 HKs and 10 RRs, while *Archaeoglobus fulgidus* has 14 HKs and 11 RRs [50]. Interestingly, the *Pyrococcus horikoshii* genome encodes for only one HK and two RRs [50]. Chemotaxis in *Halobacterium salinarum* is regulated by TCS, including HK CheA and RRs CheY and CheB [57]. Structural variations were observed in archaeal RRs from bacterial RRs, as archaeal RRs have either a receiver domain only or receiver domain and PAS and GAF domains [58]. Most RRs in archaea lack the HTH DNA-binding output domain [59]. If present, it is located at the N-terminal, while it is located at the C-terminal in bacteria [60]. We can thus infer that fusion of the output domain to the receiver domain during the evolutionary path from archaeon to eukaryotes is a revolutionary mechanism for regulating a variety of genes.

#### 4.1.3. Cyanobacteria

Cyanobacteria are oxygen-evolving photosynthetic prokaryotes that use TCS machinery to synchronize their system with the changing environmental conditions [61-63]. Cyanobacteria, such as Nostoc, synechocystis, and *O. tauri*, contain many TCS members involved in response to various environmental stimuli [64-66]. Cyanobacteria have a hybrid type of TCS with multi-domain architecture, which includes additional domains such as PAS, GAF, and PAC [61]. In *Anabaena* PCC 7120, TCS is involved in heterocyst development [66]. Most of the sensory HK proteins are cytosolic and lack the transmembrane region. Approximately 30% of cyanobacterial HKs are membrane-bound and contain the transmembrane region [67]. Analysis of cyanobacterial TCS gene signaling is vital for dissecting the signaling machinery in higher organisms, as it is believed that most eukaryotic genes originated from prokaryotes through endosymbiosis of organelles such as chloroplasts.

### 4.2. TCS in Eukaryotes

#### 4.2.1. Algae

To understand the complex signaling cascade of higher plants, it is essential to dissect the signaling machinery of

early diverging species, giving rise to land plants. Algal genome analysis is an exciting step in evolutionary study. Its endosymbiotically incorporates many organisms or is a part of another organism's system [68]. Charophyceae/streptophyte is the closest relative of land plants; interestingly, they have similar TCS machinery. Charophyceae and Embryophytes emerged as a separate group from Chlorophyta during their evolutionary journey [69-71]. Analysis of many algal genomes shows the presence of genes encoding HKs, Hpts, and type-B RRs, but, surprisingly, no members have type-A RRs [28]. *Ectocarpus* (brown algae) encode 13 HKs involved in various processes, such as EsiliHK2, containing the CHASE domain similar to plant cytokinin receptor [72]. The algal genome is an important resource for studying the signaling machinery of higher photosynthetic organisms. If we look at the domain architecture and evolutionary tree of TCS members of algae and higher plants, we can infer many similarities.

#### 4.2.2. Fungi

TCS in fungi regulates various chemotaxis processes, stress responses, virulence, morphogenesis, and red-light perception [73-75]. Yeast includes a hybrid type of HHKs in the TCS system, as most are plant or human pathogens [76]. *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, and *Candida albicans* encode different numbers of TCS genes. The Sln1-Ypd1-Ssk1 phosphorelay of *S. cerevisiae* regulates changes in osmolarity, while AbNIK1, an HK in *Alternaria brassicicola*, manages antifungal properties [77]. TCS is also involved in oxidative stress management in *C. albicans* and *A. fumigates* [78]. We included TCS machinery of early diverging fungi (EDFs) in our study to investigate how TCS genes evolved in plants from EDFs, as fungi are the connecting link between animals and plants and may play a crucial role in understanding the presence of TCS genes in plants and their absence in metazoans.

#### 4.2.3. Slime Molds

Slime molds have large, multi-domain HKs, harboring a conserved His residue to regulate the phosphorelay [79]. TCS regulates many essential processes in slime molds, including osmoregulation and fruiting body formation [80, 81]. In the cellular slime mold, *Dictyostelium discoideum*, an HK 'DhkA' regulates prestalk gene expression and terminal differentiation of prespore cells, whereas HK 'doka' is involved in osmoregulation [81]. Slime molds have fewer TCS genes than other species. However, with the advent of genomic information, more TCS genes may be found in the future.

#### 4.2.4. Bryophytes

Bryophytes are small, non-vascular plants, including mosses, liverworts, and hornworts. TCS genes are involved in phytochrome signaling and gametophore development [82-85]. Most HKs in bryophytes include a PAS domain, which is characteristically present in many other species and involved in protein-protein interactions and sensing light signals. The *Physcomitrella patens* genome encodes many

more TCS genes than angiosperms [85], many of which are homologs of cytokinin and ethylene receptors in angiosperms [86]. Thus, this genome may reveal many aspects of TCS evolution, including how and why the number of TCS genes decreased in angiosperms. The PHK1 and PHK2 genes in *Physcomitrella patens* are involved in light signaling and oxygen perception [85].

#### 4.2.5. Plants

Plants use the hybrid type of TCS system, which regulates multiple biological processes involved in growth and development, hormone signaling, circadian clock regulation, and stress responses [87]. Genome analysis of TCS in different plant species revealed the presence of various TCS genes and their changes in expression under different abiotic stresses. In many species, including lotus and *Medicago truncatula*, TCS genes are involved in root nodule formation [88, 89]. In poplar, TCS regulates cambium development [90]. Moreover, crosstalk between TCS proteins and other hormones, such as auxin, cytokinin, ethylene, and jasmonic acid, have been observed in various plant systems [91-93]. *Arabidopsis thaliana* has 49, rice has 52, and *Populus trichocarpa* has 49 TCS genes [14, 92, 93]. Among all eukaryotes, plants use advanced TCS machinery with well-developed architecture as their signaling mechanism, as they are immobile and need efficient machinery to cope with the environmental signals.

### 5. EVOLUTION OF KEY PLAYERS IN THE TCS SYSTEM

It is evident that different components of the TCS signaling cascade emerged at different times in the evolutionary pathway in kingdoms. TCS proteins interact with various other proteins outside the TCS family, such that some crosstalk may occur between the TCS and other signaling cascades present in an organism [94-97]. To understand the evolutionary perspective of TCS systems, we investigated the domain architecture, the number of transmembrane helices, and phylogenetic outlook of the TCS system in prokaryotes and eukaryotes. For the analysis, we have retrieved the protein sequences from various publicly available databases like NCBI ([www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)), TAIR ([www.arabidopsis.org](http://www.arabidopsis.org)), TIGR ([rice.plantbiology.msu.edu](http://rice.plantbiology.msu.edu)), JGI DOE ([genome.jgi-psf.org](http://genome.jgi-psf.org)), and Dictybase ([dictybase.org](http://dictybase.org)).

#### 5.1. Histidine Kinase

Histidine kinase is the primary sensor protein of the TCS signaling cascade; it is responsible for initiating the cascade by perceiving the signal. Histidine kinases can act as a photoreceptor, hormone signaling receptor, or osmosensor [98-100]. The N-terminal sensory domain is diverse and can form various distinct domains, including PAS, GAF, cAMP, HAMP, or CHASE, depending on its structure and function. The sensing domain is exposed to the extracellular or periplasmic region. Moreover, the N-terminal sensing module is less conserved than the catalytic domain of HK. The presence of a conserved histidine containing motif in different

photoreceptors, osmoreceptors, and hormone receptors confirms the conservation of HKs through evolution [98, 101].

Hybrid HKs are generally transmembrane proteins with multiple domains, such as CHASE, HK domain (HisKA), ATPase domain, and receiver domain, but may also be soluble cytosolic where it lacks these domains [102]. The receiver domain contains a conserved DDK domain that includes a conserved Asp residue involved in phosphorelay. Most HKs are functionally redundant and localized either on the plasma membrane or endoplasmic reticulum [103, 104]. They have both phosphorylation and dephosphorylation activity. AHK4, an Arabidopsis cytokinin receptor, behaves as both phosphatase and dephosphatase, depending on the presence or absence of cytokinin. Histidine kinases have maximum activity at pH 6.5, which is a characteristic pH of ER [105]. Most HKs act as a homodimer or heterodimer, where one HK unit catalyzes the transphosphorylation of other units [106]. However, some HKs act as a monomeric unit [107]. Histidine kinases are highly homologous proteins [108, 109]. Histidine kinase has traveled a long journey from prokaryotes to eukaryotes to efficiently perceive a diverse range of signals, which are passed to downstream members.

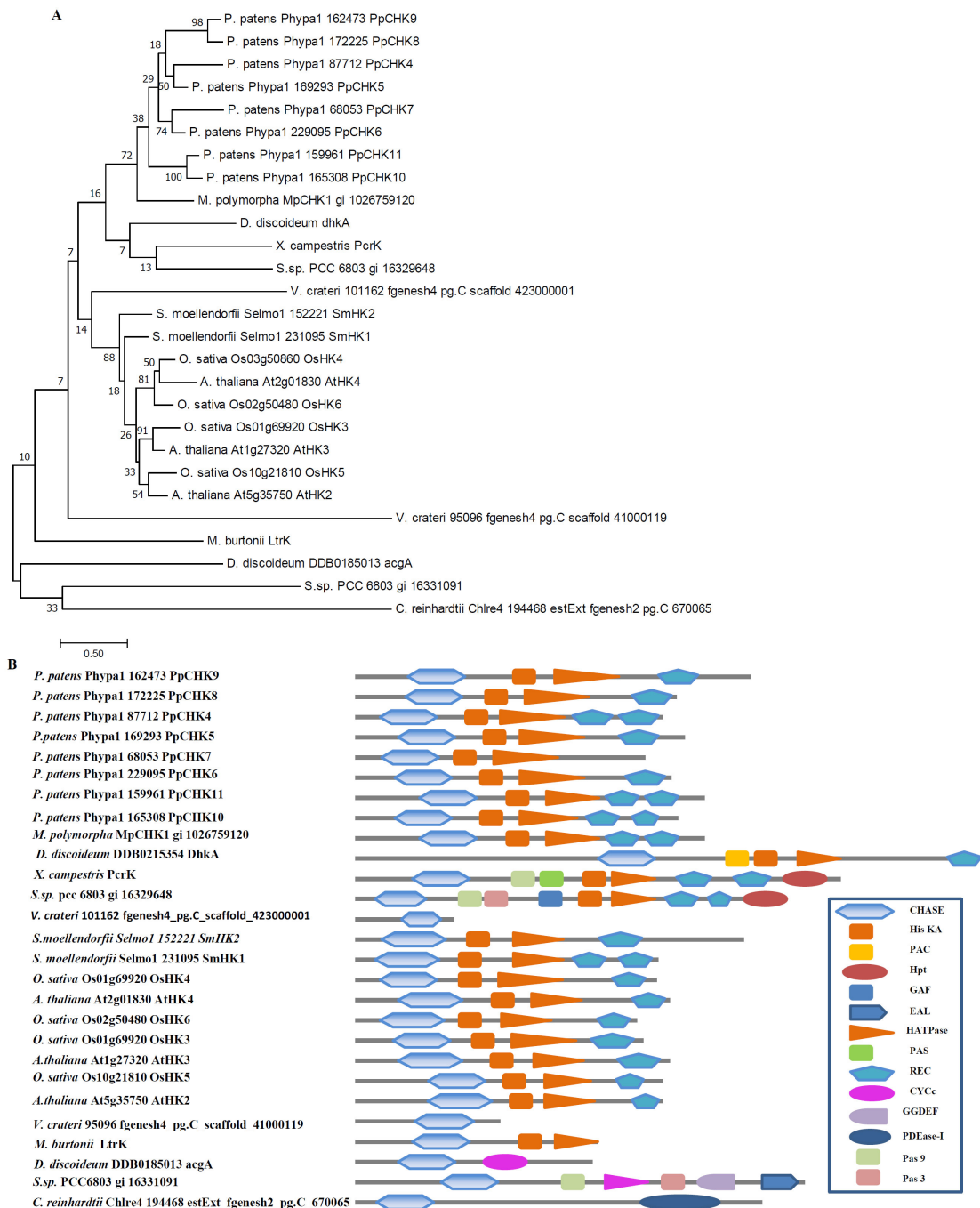
#### 5.2. Chase Domain

Cyclases/histidine kinases associated sensory extracellular (CHASE) is an N-terminal, extracellular sensing domain present in many receptors with HK and nucleotide cyclase domains in bacteria, lower eukaryotes, and plants [110]. The N-terminal sensing domain is more diverse than the conserved catalytic domain of HK and is involved in signal perception. The binding of CHASE with its ligands causes conformational changes in the receptor, which leads to autophosphorylation at the conserved His residue of the HK protein. Plants acquired the CHASE domain through chloroplasts during the evolutionary endosymbiotic event between cyanobacteria and plants [111, 112]. CHASE is present in some plant species but not others, *e.g.*, of the six HKs in *Oryza sativa* (OsHK1, OsHK2, OsHK3, OsHK4, OsHK5, and OsHK6), four (OsHK3, OsHK4, OsHK5, and OsHK6) contain the CHASE domain. An evolutionary proteomics study revealed that few amino acids in the CHASE domain are conserved in various species and are essential for binding with distinct ligands [113]. Thus, the CHASE domain is highly specific for its ligands. In-plant cytokinin receptors, the CHASE domain shows a high degree of specificity among different classes of cytokinins, which suggests that the binding pocket of CHASE is highly specific for its ligands and cannot accommodate other molecules. Only small ligands, such as free cytokinin bases, can bind to it.

Many phytopathogenic bacteria evolved plant hormone receptors for counteracting host immune response, *e.g.*, *Xanthomonas campestris*; phytopathogen has a receptor kinase PerK, which can recognize plant-derived cytokinins [22]. Phylogenetic analysis of the TCS system indicated that the CHASE domain evolved only in land plants, including mosses, lycophytes, and higher plants [28]. However, there are a few exceptions, including *D. discoideum*, a non-plant eukary-

ote with a CHASE domain as a signal receiving module. While the algal genome lacks the gene encoding for the CHASE domain, some studies have confirmed the presence of the CHASE domain in a few archaea and phytopathogenic bacterial species [56]. We have created a phylogenetic tree of full-length HK proteins containing the CHASE do-

main using MEGA7 (Fig. 2A). We analyzed the domain architecture of the CHASE receptor, including HKs, to determine the involvement of additional domains (Fig. 2B). The *Selaginella* CHASE domain is closely related to that of higher plants, such as rice and Arabidopsis.



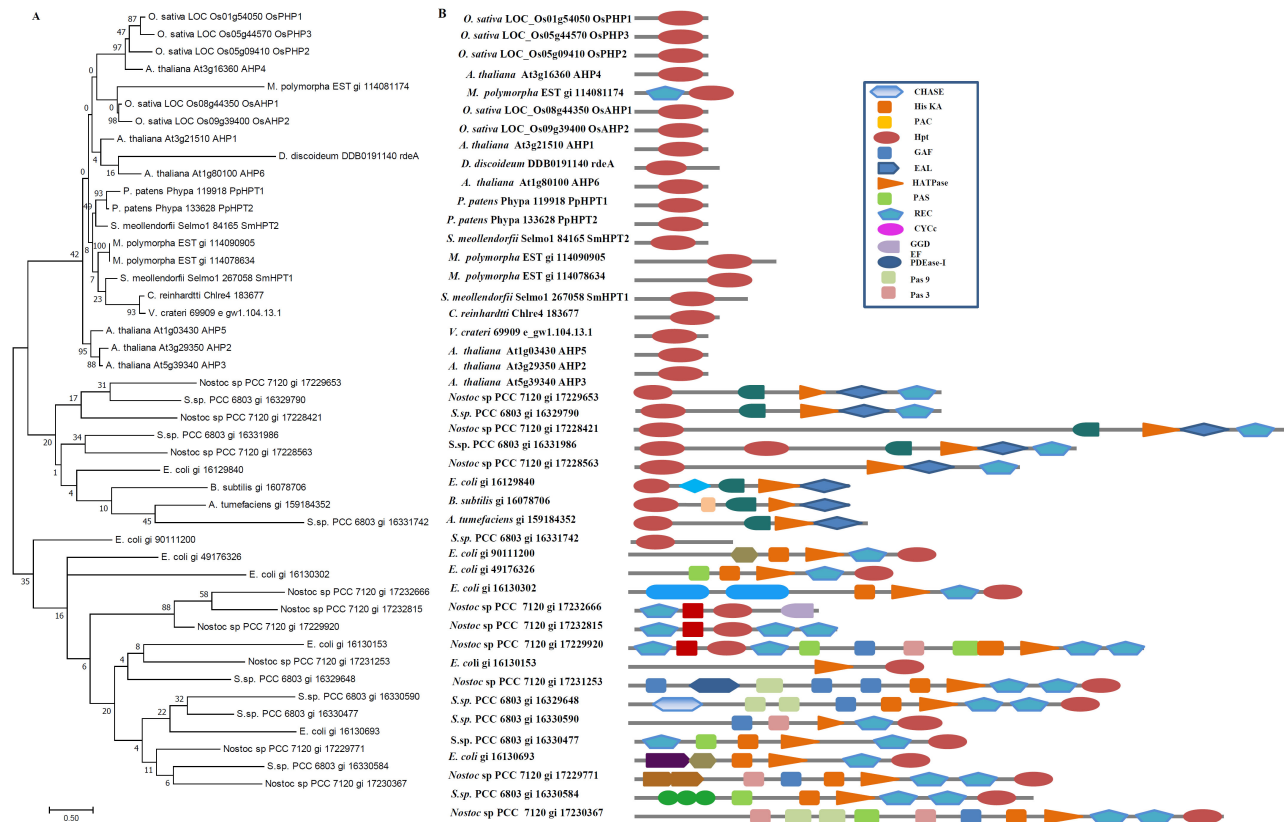
**Fig. (2).** (A) Molecular Phylogenetic analysis of the CHASE domain and kinase domain across genera. The tree was built using MEGA7 by the Maximum Likelihood method. (B) Expansion of distinct domains other than key conserved domains in the histidine kinases of various organisms. (A higher resolution / colour version of this figure is available in the electronic copy of the article).



### 5.3. Histidine-containing Phosphotransfer Proteins

Histidine-containing phosphotransfer proteins are present in all organisms, from bacteria to eukaryotes [113]. In prokaryotes, Hpts are covalently attached to HK at its C-terminal end, but in eukaryotes, it is slowly separated as an individual protein that can communicate between the two members, HK and RR. Hence, it serves as a mediator protein between the two units. There are no reports of eukaryotic HHK with a fused Hpt domain, indicating its evolution as a separate protein in eukaryotes. A fused Hpt domain was first discovered in the *E. coli* ArcB HK protein [41, 114]. Hpts work as a monomeric unit and are localized both in the cytoplasm and nucleus. They are crucial from an evolutionary perspective as they act as a diverging point in the TCS signaling and are responsible for interacting with proteins outside the TCS family, such as cytokinin response factors (CRFs) for regulating cytokinin signaling and ETR1 for managing ethylene response [115]. In almost all photosynthetic organisms, Hpts are of single domain. They can be classified into two categories based on the nature of conserved residue present within them (1) authentic histidine phosphotransfer proteins (Ahp) that contain a conserved His residue that is phosphorylated by HKs, and (2) pseudo histidine phospho-

transfer proteins (Php) that lack conserved His residue. The Pbps or non-canonical Hpts are only found in angiosperms and gymnosperms. As compared to the expansion of HKs and RRs genes, Hpts are more conserved [116]. They do not exhibit catalytic domains and can perform both phosphorylation and dephosphorylation of other proteins; thus, acting as a feedback switch in the TCS pathway. ‘Spo0B’ was the first Hpt protein discovered in bacteria *Bacillus subtilis*, and is involved in sporulation [117]. Hpts initiate the transcription of their downstream target genes, including type-A RRs. Hpts of land plants are closely related to Hpts of green algae (Charophyceae). Ypd1, an Hpt protein, is essential for viability in yeasts, including *Saccharomyces cerevisiae*, *Neurospora crassa*, *Aspergillus nidulans*, and *Cryptococcus neoformans*, but not essential for cell viability in *Candida albicans* [118, 119]. Ypd1 in *Candida albicans* is involved in phytochrome-dependent light signaling [74]. Phylogenetic analysis of full-length Hpt proteins revealed its ubiquitous nature in almost all domains of life (Fig. 3A). Domain analysis of Hpts showed that Hpt resided within HKs, but during the evolutionary journey, it started functioning as an individual protein (Fig. 3B). This divergence of Hpt from HK enabled higher organisms to fine-tune their signals under varied circumstances.



**Fig. (3).** (A) Molecular Phylogenetic analysis of histidine-containing phosphotransfer proteins (Hpts) by Maximum Likelihood method on the JTT matrix-based model. Evolutionary analyses were conducted in MEGA7. (B) Domain architecture of histidine-containing phosphotransfer proteins from various organisms. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

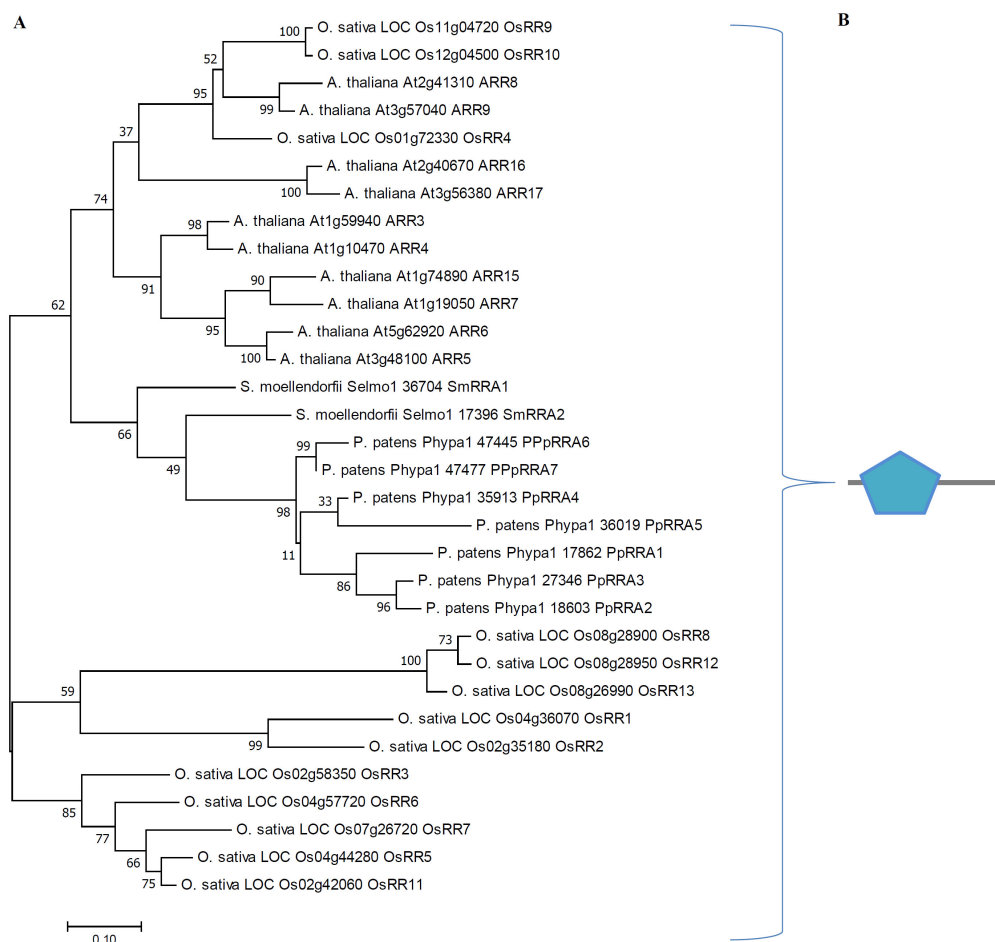
## 5.4. Response Regulators

Response regulators mediate signal responses. The output unit in RRs is more diverse than the input unit, which was more conserved during evolution. This is because the output unit has to mediate diverse responses to ensure the functionality of the organism. From algae to higher plants, there has been vast expansion within RR proteins, such that RRs are significant in number and more diverse than HKs and Hpts. Response regulators contain conserved Asp and Lys residue in their receiver domain [14]. Response regulators can be categorized into different subfamilies based on their function and domain architecture [120]. If we look at the phylogenetic distribution and evolutionary pattern of RRs, different RRs evolved at different points of the evolutionary lineage.

### 5.4.1. Type-A RRs

Type-A RRs (ARR) accommodate an Asp-containing phosphoaccepting receiver domain on their N-terminal and a

short C-terminal effector domain. They may be cytosolic or nuclear-localized and act as negative regulators of various signaling pathways, such as cytokinin signaling [121-123]. Furthermore, they participate in the negative feedback pathway of the TCS. ARR interacts with type-B RRs and Hpts to dephosphorylate them and thus act as dephosphatases; for example, in cytokinin signaling, many ARRs act as redundant negative regulators of cytokinin signaling [122]. Phylogenetic investigation suggests that ARRs, along with the CHASE domain, were recruited during the evolution of land plants [29, 30]. Type-A RRs might have evolved from type-C RRs by mutations in their promoters [124]. Thus, this negative feedback checkpoint monitors the TCS signaling cascade. Type-A RRs also interact with many other proteins, apart from the TCS pathway protein, regulating different signaling cascades. *e.g.*, WUS, a transcription factor. Phylogenetic analysis of a few representatives of each kingdom using MEGA7 is shown in Fig. (4A). Full-length type A RR protein sequences were used to construct the phylogenetic tree. Domain architecture is shown in Fig. (4B).



**Fig. (4).** (A) Molecular Phylogenetic analysis of Type A RRs from different organisms. The tree was constructed in MEGA 7 by the Maximum Likelihood method using the JTT matrix. (B) Domain architecture of Type A RR. All the organisms had only one domain, *i.e.*, receiver domain. (A higher resolution / colour version of this figure is available in the electronic copy of the article).



### 5.4.2. Type-B RRs

Type-B RRs (BRR) is similar to ARR in domain architecture and contain an N-terminal phosphoaccepting receiver domain containing a conserved Asp residue and an MYB DNA-binding C-terminal domain [125-127]. Thus, BRRs act as transcription factors for the regulation of various types of genes, including ARRs, for regulating diverse processes [124]. In plants like Arabidopsis, BRRs act as positive regulators of cytokinin signaling and regulate the transcription of ARRs. Type-B RRs are specific to photoautotrophic species, including algae and plants [128] (Fig. 5A). Domain analysis and sequence analysis revealed that some BRRs lack a DNA-binding domain and canonical Asp residue, which confirms the early invasion of BRRs during phylogeny (Fig. 5B). Full-length protein sequences were used as a query in MEGA7.

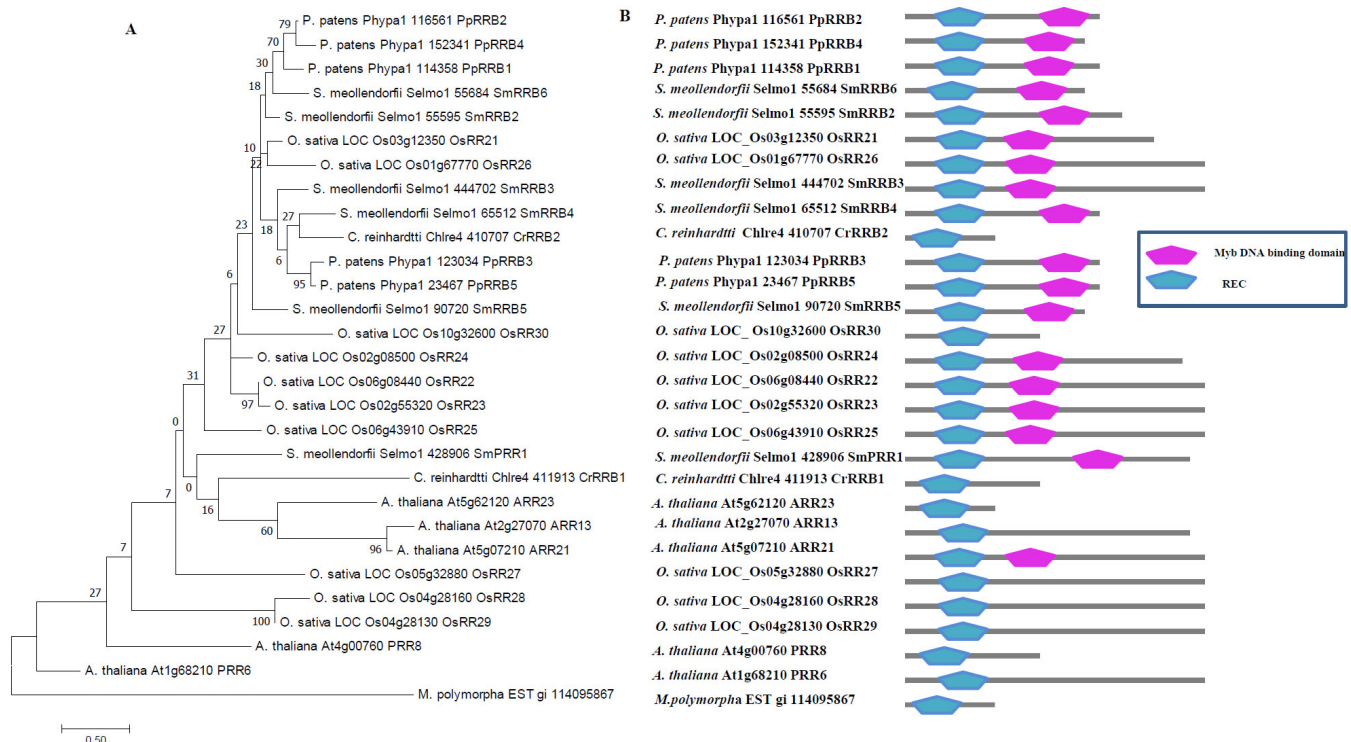
### 5.4.3. Type-C RRs

Type-C RRs (CRRs) contain an N-terminal Asp containing the receiver domain but lack an MYB DNA-binding C-terminal domain [128]. These degenerate RRs are similar to the RR domain of HKs [129, 130], which were also supported by the presence of an ATPase domain in two species RRs, *Selaginella moellendorffii* and *Picea abies* [30]. Some CRRs act as phosphatases, similar to HKs, strengthening

their interconnection [131, 132]. Type-C RRs were first introduced by Schaller *et al.* [129]. While their proper function has not been characterized, some studies have revealed their role in plant developmental processes [131, 132]. Many CRRs have changes in the DDK motif, such that they may lie between ARRs and BRRs in the phylogeny. Phylogenetic analysis of some CRRs was undertaken using the Maximum Likelihood method on the JTT matrix-based model in MEGA7 using full-length RR C protein sequences (Fig. 6A). Domain architecture of different type C RRs has been depicted in Fig. (6B).

### 5.4.4. Pseudo Response Regulators (PRRs)

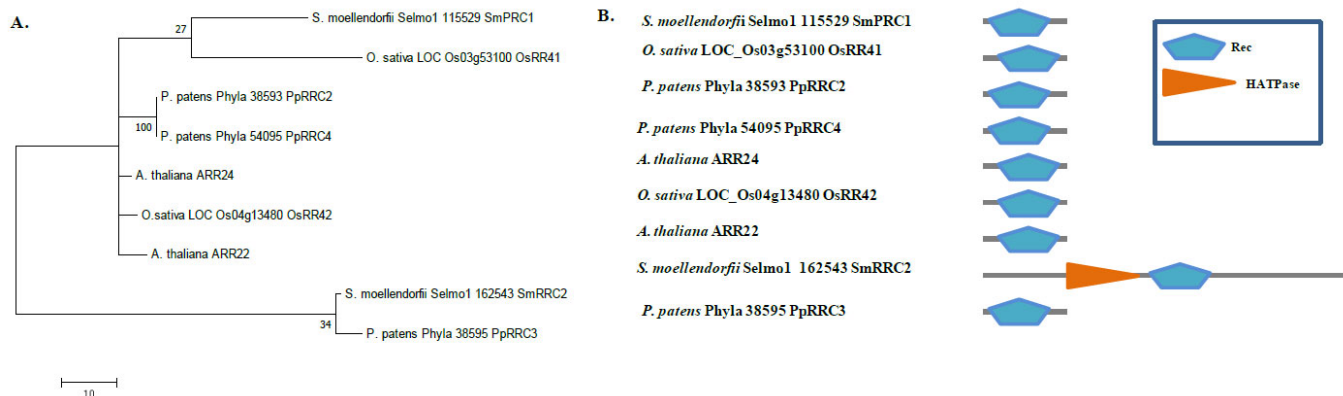
Plants have evolved a unique class of RRs known as pseudo response regulators (PRRs) because they lack the conserved Asp residue in their N-terminal receiver domain. The conserved Asp residue is replaced by glutamate [133-136]. PRRs contain two domains (1) a receiver domain that lacks the conserved Asp residue and (2) a Constans/Constans-like/TOC1 (CCT) domain. PRRs are present only in higher plants and play a crucial role in circadian clock regulation and light signaling [135-138]. They maintain a wide range of biological processes, such as stomatal opening and closing, flowering, and changes in photosynthetic activities [139-141]. Through their domain architecture and conserved motifs analysis, we can conclude that angiosperm PRRs are



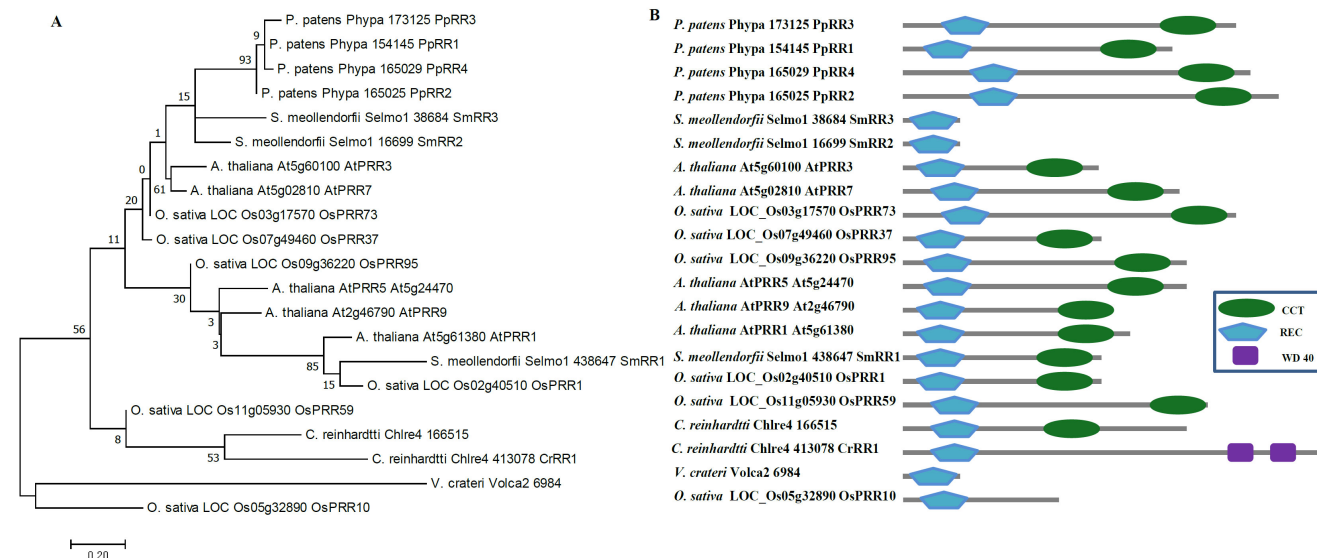
**Fig. (5).** (A) Molecular phylogenetic analysis of Type B RRs by Maximum Likelihood method. Evolutionary analyses were conducted in MEGA7. (B) Domain architecture of Type B RRs of various organisms. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

closely related to moss PRRs [142]. In Arabidopsis, five PRR genes are present-PRR1 (TOC1), PRR3, PRR5, PRR7, PRR9-which regulate the Arabidopsis circadian clock [133]. OtTOC1, a PRR in green algae (*Ostreococcus tauri*), has aspartic acid in its receiver domain, but higher land plants have replaced this Asp residue with glutamate during evolution [143]. By analyzing green algae and moss PRRs, it is clear that PRRs originated from authentic RRs. PRRs have a role in a variety of endogenous processes, such as photosynthesis and cell division [144, 145]. We conclude that ARRs and BRRs are closer to each other through phylogenetic

study and fall in one clade along with PRRs while CRRs are on other clade. There are three significant subclades of ARRs, BRRs, and PRRs, with BRRs and PRRs in one subclade [146]. PRRs were separated from their relative BRRs and acquired some additional domains because few BRRs lack the conserved Asp residue [146]. Phylogenetic analysis of full-length CRR proteins were undertaken based on the Maximum Likelihood method using JTT matrix-based model in MEGA7 (Fig. 7A). The domain architecture of PRRs was studied to put more light on these response regulators (Fig. 7B).



**Fig. (6).** (A) Molecular Phylogenetic analysis of Type C RRs by Maximum Likelihood method on the JTT matrix-based model. Evolutionary analyses were conducted in MEGA 7. (B) Domain architecture of Type C RRs of various organisms. (A higher resolution / colour version of this figure is available in the electronic copy of the article).



**Fig.(7).** (A) Molecular Phylogenetic analysis of PRRs by Maximum Likelihood method using the JTT matrix-based model. Evolutionary analyses were conducted in MEGA 7. (B) Domain architecture of Type PRRs of various organisms. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

#### 5.4.5. Transmembrane Segments

Although most HKs are membrane-bound and thus have the transmembrane region, few are cytosolic and soluble. Nevertheless, the transmembrane region might play a crucial role in the propagation of the signal. The transmembrane region contains a few essential conserved residues responsible for changes in the conformation of the receptor upon receiving the stimulus. Mutation in these residues may lead to the disruption or constitutive signaling of those receptors. In *Arabidopsis* cytokinin receptor AHK2, Leu552 is a crucial replacement that induces the conformational changes in the receptor, which are similar to those achieved by its binding with cytokinin, and thus shows constitutive expression [147]. The number of times a transmembrane receptor passes the membrane differs between different classes of proteins. Like in *Arabidopsis*, AHK2 and AHK3 are three-pass transmembrane proteins, whereas AHK4 is a two-pass protein [148], while in rice, OsHK3, OsHK4, and OsHK6 are two-pass transmembrane proteins, and OsHK5 is a five-pass transmembrane protein. We need to search for essential amino acids and correlated their differences in various transmembrane segments and functions.

#### CONCLUSION AND FUTURE PERSPECTIVES

Agriculture is facing many stumbling blocks due to the changing environment, soil erosion, loss of biodiversity, and increasing food demand. To fulfill the growing population's demand, the tolerance level against the stresses of our major food crops needs to improve. It is essential to study the mechanisms of signal perception in plants and how those mechanisms evolved. When life originated in an aquatic environment, different signaling mechanisms also evolved, helping organisms to sense environmental clues. As life became more complex, these signaling networks underwent adaptations to improve system regulation. Both prokaryotes and eukaryotes are diverse in terms of physiology, internal complexity, and survival under different conditions. TCS has evolved as an interesting signaling cascade for the regulation of numerous processes from lower prokaryotes to higher eukaryotes [149-154]. It has recruited changes in its machinery to maintain its existence with the evolution of organisms. We observed that TCS engages protein phosphorylation by HKs conserved in the kingdom to transfer the phosphor-message to another protein when one protein is phosphorylated while the other is non-phosphorylated. To pass any signal, coordination between the signaling units is of utmost importance. The TCS may modify itself to perceive different types of ligands or environmental clues faced during evolution and accordingly incorporate signaling units and proteins. Through phylogenetic study and domain architecture analysis, we infer that various members of the MSP signaling appear at different time points of the evolutionary tree. CHASE and BRRs came first, while ARRr, the negative regulators, first emerged in land plants. CRRs and ARRr have similar architecture. Domain architecture of bacterial and archaeon TCS machinery reveals variation in the output unit of the circuitry. Most TCS protein genes are recruited in the eukaryotic genome through horizontal gene transfer from prokaryotes. Different TCS proteins have

evolved and become embedded in the signaling cascade over time. There is much to explore about the players involved in the signaling cascade, *i.e.*, HKs and RRr. Expansion of the RR gene family, relative to HKs and Hpts, indicates that RRr may be regulated by some additional upstream players (not just TCS members). The diverse C-terminal end of RRr is responsible for the varying responses to different stresses. TCS evolved with the adaptation of eukaryotic organisms over time. The His-Asp-His-Asp phosphorelay provides multi-step checkpoints for cascade regulation. The molecular basis of the co-evolution builds a framework for understanding the basis of MSP. Each TCS gene serves as a key candidate for the production of stress-tolerant and genetically advanced crops like in rice, maize, *etc* [16, 155, 156].

#### CONSENT FOR PUBLICATION

Not applicable.

#### FUNDING

DS acknowledges the Senior research fellowship received from DBT. Research grants received to the laboratory from the Department of Biotechnology, Department of Science and Technology, Government of India, and Indo-US Science and Technology Forum (IUSSTF) *via* Indo-US Advanced Bioenergy Consortium (IUABC) are duly acknowledged.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

#### ACKNOWLEDGEMENTS

DS acknowledges Senior research fellowship received from DBT.

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