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Letter to the editors**Megaviruses: an involvement in phytohormone receptor gene transfer in brown algae?**Samar Kabbara¹, Baptiste Bidon¹, Jaafar Kilani¹, Thomas Dugé de Bernonville², Marc Clastre², Vincent Courdavault², J. Mark Cock³, Nicolas Papon^{1*}¹Groupe d'Etude des Interactions Hôte-Pathogène, GEIHP, EA3142, UNIV Angers, SFR 4208 ICAT, Angers, France²Biomolécules et Biotechnologies Végétales, BBV, EA2106, Université François Rabelais de Tours, Tours, France³Algal Genetics Group, UMR 8227, Integrative Biology of Marine Models, Station Biologique de Roscoff, Sorbonne Université, UPMC Université Paris 06, CNRS, Roscoff, France.*Author for correspondence: nicolas.papon@univ-angers.fr

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Histidine kinases are a prominent family of sensing proteins that perceive and transduce a broad range of external stimuli in both prokaryotes and eukaryotes (Osakabe *et al.*, 2013 ; Mascher *et al.*, 2006, Hérivaux *et al.*, 2016). These proteins are particularly widespread in bacteria, fungi, plants, amoebae, and SAR (Stramenopiles, Alveolates, and Rhizaria) (Kabbara *et al.*, 2019). Receptors of plant hormones (phytohormones) are one of the most documented types of histidine kinases. This group of proteins includes cytokinin and ethylene receptors, which are known to be involved in plant development but also to respond to biotic and abiotic stress (Zdarska *et al.*, 2015). For a long time, cytokinin and ethylene receptors were believed to be restricted to Archaeplastida (green lineage), but recent phylogenomic studies strongly suggest the presence of these types of phytohormone sensing proteins in bacteria, early diverging fungi, amoebae, and SAR (Hérivaux *et al.*, 2017 ; Kabbara *et al.*, 2018 ; Kabbara *et al.*, 2019 ; Papon and Binder, 2019).

In SAR, whereas Alveolates appear to only harbor putative ethylene receptors, both ethylene and cytokinin receptor homolog genes were detected in the genomes of some Stramenopile species, notably those of brown algae (Kabbara *et al.*, 2019). The genome of the model brown alga *Ectocarpus* sp. encodes 13 histidine kinases (Figure 1A), including EsiliHK2 which is similar to plant cytokinin receptors. Other prominent groups of histidine kinases categorized in the *Ectocarpus* sp. genome include the phytochrome type (EsiliHK3-6-7-8-9) and the MASE1 type (EsiliHK10-12) receptors (Kabbara *et al.*, 2019).

One of the singularities of *Ectocarpus* biology is that it can be infected by marine viruses belonging to the phaeovirus family (Van Etten *et al.*, 2002), particularly *Ectocarpus siliculosus* virus 1 (EsV-1) (Delaroque *et al.*, 1999). This virus is lysogenic and integrates its large DNA genome (335,593 bp) into the *Ectocarpus* genome during the infection cycle (Delaroque *et al.*, 1999). Surprisingly, six of the 231 predicted EsV-1 open reading frames correspond to histidine kinases (Delaroque *et al.*, 2000 ; Delaroque *et al.*, 2001). Because virus genomes are not known to usually encode histidine kinases, we investigated this feature more deeply (Figure 1B).

48 We found that four of the six predicted EsV-1 histidine kinases could be categorized into
49 previously described groups of eukaryotic histidine kinases, according to a previous classification
50 (Kabbara *et al.*, 2019). For example, the EsV-1-186 predicted protein contains not only the
51 canonical domain arrangement of eukaryotic histidine kinases but also a Membrane-Associated
52 Sensor 1 (MASE1) N-terminus composed of seven transmembrane regions (Figure 1B). MASE1-
53 containing histidine kinases are also found in bacteria and early diverging plants (Kabbara *et al.*,
54 2019 ; Mascher *et al.*, 2006) but their function remains unknown. Similarly, the EsV-1-65 predicted
55 protein corresponds to previously described light sensing phytochromes (Delaroque *et al.*, 2001).
56 However, the most interesting predicted histidine kinases are EsV-1-65 and EsV-1-112. Indeed, EsV-
57 1-65 harbors an N-terminal **C**yclases/**H**istidine kinases **A**ssociated **S**ensing **E**xtracellular (CHASE)
58 domain (Anantharaman and Aravind 2001; Mougel and Zhulin 2001). This CHASE domain is typically
59 bordered by two transmembrane regions and is known to be essential in plants for cytokinin
60 perception and signal transduction (Gruhn *et al.* 2014). In addition, the EsV-1-112 predicted protein
61 contains an N-terminus composed of three hydrophobic transmembrane helices (green bars in
62 Figure 1B) harbouring conserved amino-acids (green stars in Figure 1B), that have been
63 demonstrated to be required for ethylene binding in plants and cyanobacteria (Wang *et al.*, 2006 ;
64 Lacey and Binder, 2016).

65 Genome analysis previously provided evidence that six of the *Ectocarpus* sp. histidine genes
66 (i.e. EsiliHK3, EsiliHK4, EsiliHK5, EsiliHK10, EsiliHK11 and EsiliHK13) are located within integrated
67 viral fragments (Delaroque and Boland, 2008 ; Cock *et al.* 2010 ; Kabbara *et al.*, 2019) that are
68 highly similar to EsV-1. These six genes should therefore be considered as viral rather than algal
69 and we propose to rename them EsiliHK3^V, EsiliHK4^V, EsiliHK5^V, EsiliHK10^V, EsiliHK11^V and EsiliHK13^V
70 (Figure 1C), to highlight their origin. Here we were interested in deciphering the phylogenetic
71 relationships between the *Ectocarpus* sp. and EsV-1 predicted histidine kinases. A phylogenetic tree,
72 generated from a multiple alignment of all the predicted *Ectocarpus* sp. and EsV-1 histidine kinase
73 sequences, indicated that, with the exception of EsiliHK6, all of the predicted *Ectocarpus* sp.
74 histidine kinases tended to cluster with an EsV-1 protein, notably cytokinin receptor homologs,
75 ethylene receptor homologs, MASE1-containing histidine kinases, and phytochromes (Figure 1C).
76 Taken together, these observations suggest common origins for most *Ectocarpus* sp. and EsV-1
77 histidine kinase genes.

78 In conclusion, we show here that, out of the six predicted histidine kinase genes in the
79 genome sequence of EsV-1 (Delaroque *et al.*, 2000 ; Delaroque *et al.*, 2001), two share domain
80 organisation and sequence homology with plant cytokinin and ethylene receptors. In addition,
81 homologs of both types of phytohormone sensing protein were also found in the genome of the
82 EsV-1 host, *i.e.* the filamentous brown alga *Ectocarpus* sp.. We thus hypothesise that, as recently
83 observed for other gene families (Macaisne *et al.*, 2017), gene exchanges between the EsV- 1 and
84 *Ectocarpus* sp. lineages contributed significantly during evolution to emergence and diversification of
85 these organisms, histidine kinase gene repertoires. In a broader context, this study provides the first
86 strong arguments suggesting horizontal transfer of phytohormone receptor homologs between
87 megaviruses and brown algae. However, we did not detect any homologs of EsV-1 and *Ectocarpus*
88 sp. phytohormone receptors in other viral, eukaryotic, or prokaryotic genomes. This precludes any
89 speculation about the precise origin of these genes but also the determination of the initial direction
90 of these horizontal gene transfer events (virus > alga or alga > virus).

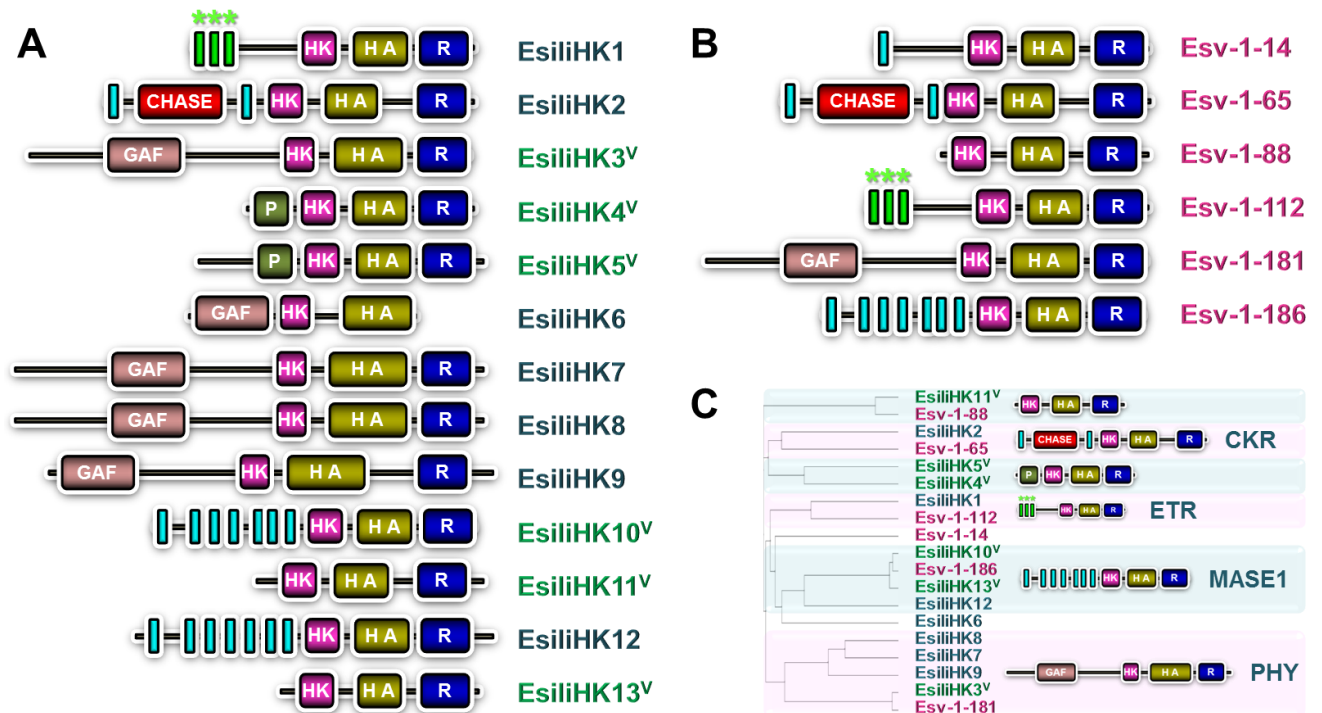
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 148
 149 **Figure 1. Domain organization and phylogenetic relationship between *Ectocarpus* sp. and EsV-1 predicted histidine kinases.**
 150 **A. Predicted structure of *Ectocarpus* sp. histidine kinases. B. Predicted structure of EsV-1 histidine kinases. C. Phylogeny**
 151 **estimation of histidine kinase predicted protein sequences.** A representative structure is provided for each defined histidine kinase
 152 group. *Ectocarpus* sp. and EsV-1 sequences were previously compiled in Kabbara *et al.*, 2019 and Delarouque *et al.*, 2001, respectively.
 153 Domain arrangement was predicted using SMART software. The multiple sequence alignment and the tree (Maximum Likelihood,
 154 Bootstrap of 50) were generated with Clustal omega and MEGA softwares, respectively. Sequence accession numbers: CBN79297.1
 155 (EsiliHK1), CBJ26502.1 (EsiliHK2), CBN80472.1 (EsiliHK3), CBN80469.1 (EsiliHK4), CBN80306.1 (EsiliHK5), CBJ28288.1 (EsiliHK6),
 156 CBJ33980.1 (EsiliHK7), CBJ33173.1 (EsiliHK8), CBJ31548.1 (EsiliHK9), CBN80477.1 (EsiliHK10), CBN80390.1 (EsiliHK11), CBJ25730.1
 157 (EsiliHK12), CBJ33468.1 (EsiliHK13), NP_077499 (Esv-1-14), NP_077550.1 (Esv-1-65), NP_077573.1 (Esv-1-88), NP_077597.1 (Esv-1-
 158 112), NP_077666.1 (Esv-1-181), NP_077671.1 (Esv-1-186). Abbreviations: CHASE, Cyclases/Histidine kinases Associated Sensing
 159 Extracellular; CKR, cytokinin receptor; ETR, ethylene receptor; GAF, cGMP-specific phosphodiesterases-Adenylyl cyclases-Fh1A; HA,
 160 histidine kinase-like ATPase catalytic domain; HK, Histidine Kinase A (dimerization/phosphoacceptor) domain; MASE1, Membrane-
 161 Associated Sensor 1; P, period circadian protein-aryl hydrocarbon receptor nuclear translocator protein-single-minded protein; PHY,
 162 phytochrome; R, receiver domain.