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COMMENTARY

Systematic Nomenclature for GGDEF and EAL Domain-Containing Cyclic Di-GMP Turnover Proteins of *Escherichia coli*

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In recent years, *Escherichia coli* has served as one of a few model bacterial species for studying cyclic di-GMP (c-di-GMP) signaling. The widely used *E. coli* K-12 laboratory strains possess 29 genes encoding proteins with GGDEF and/or EAL domains, which include 12 diguanylate cyclases (DGC), 13 c-di-GMP-specific phosphodiesterases (PDE), and 4 "degenerate" enzymatically inactive proteins. In addition, six new GGDEF and EAL (GGDEF/EAL) domain-encoding genes, which encode two DGCs and four PDEs, have recently been found in genomic analyses of commensal and pathogenic *E. coli* strains. As a group of researchers who have been studying the molecular mechanisms and the genomic basis of c-di-GMP signaling in *E. coli*, we now propose a general and systematic *dgc* and *pde* nomenclature for the enzymatically active GGDEF/EAL domain-encoding genes of this model species. This nomenclature is intuitive and easy to memorize, and it can also be applied to additional genes and proteins that might be discovered in various strains of *E. coli* in future studies.

More than 10 years ago, it was demonstrated that GGDEF domains can produce and EAL domains can degrade the bacterial second messenger cyclic di-GMP (c-di-GMP) (1–4). With these assignments, it also became clear that bacterial genomes—in particular, those of gammaproteobacteria—usually contain multiple genes encoding these diguanylate cyclases (DGC) and c-di-GMP phosphodiesterases (PDE) (5, 6). Crystal structures of GGDEF and EAL domains have been elucidated, and studies of structure-function relationships have identified the key amino acid residues required for substrate and cation binding and catalysis (7). This also allowed identification of a subset of GGDEF and EAL (GGDEF/EAL) domain proteins, in which these key amino acids are not conserved, as "degenerate" and enzymatically inactive. In a few cases, it could be demonstrated that these degenerate GGDEF/EAL domain proteins have alternative functions based on direct interactions with other macromolecules (8–11). A subset of proteins combine GGDEF and EAL domains in a single polypeptide, where one domain is usually enzymatically active and the other is degenerate and plays a regulatory role in these "composite" proteins (3). Most GGDEF/EAL domain proteins also contain N-terminal sensory input domains that control their output activities, and a majority are localized or anchored in the cytoplasmic membrane via their membrane-intrinsic or periplasmic sensory domains (12).

In studies of the molecular principles and physiological functions of c-di-GMP signaling, *Escherichia coli* has served as one of a few model species (13, 14). The commonly used *E. coli* K-12 laboratory strain has a total of 29 proteins with GGDEF and/or EAL domains, including 12 and 10 proteins featuring the GGDEF and EAL domains alone, respectively, and 7 composite proteins carrying both domains. Based on direct measurements of purified proteins and/or the presence of key conserved amino acids and their elimination by point mutations, DGC and PDE activities can be assigned to 12 and 13 proteins, respectively, whereas 4 of the 29 proteins can be classified as degenerate GGDEF/EAL proteins (Table 1). Genes involved in c-di-GMP signaling have also been studied in pathogenic *E. coli*, i.e., in uropathogenic *E. coli* (UPEC) (42), and two additional genes encoding PDEs have been detected in an enterohemorrhagic *E. coli* (EHEC) strain (38) and a meningitis-associated *E. coli* strain (39). Together with a recent analysis of genome sequences of 61 *E. coli* strains (29), which included commensal as well as pathogenic strains of the major pathotypes and phylogroups, a total of two additional GGDEF domain proteins and four more EAL domain proteins have been identified that are not found in *E. coli* K-12. On the basis of the presence of the key residues involved in enzymatic activities, these proteins should be active DGCs and PDEs (see an accompanying paper [29] in this issue).

Being aware that a systematic nomenclature of the many *E. coli* genes encoding DGCs and PDEs might eventually be useful, most researchers have refrained from renaming single genes and proteins involved in c-di-GMP signaling in *E. coli* and have used the preliminary *y* designations instead, even though these were difficult to memorize and certainly not popular in oral scientific presentations. However, on the basis of the finding that the DGC YdeH is regulated by zinc, it was recently renamed "DgcZ" (23). Also, the newly identified genes encoding DGCs and PDEs in non-

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TABLE 1 Novel designations for GGDEF/EAL domain-encoding genes of *E. coli*

Gene name	b no.	UniProt entry	New gene name	Other gene name[d]	Domain architecture[a]	Comment and/or reference(s)[e]
Genes encoding diguanylate cyclases (intact GGDEF domains)						
yaiC	b0385	P0AAP1	*dgcC*	*adrA**	MASE2[b]-GGDEF	12, 15–17
ycdT	b1025	P75908	*dgcT*		MASE4[b]-GGDEF	(18)
ydaM	b1341	P77302	*dgcM*		PAS-PAS-GGDEF	19–21
yddV	b1490	P0AA89	*dgcO*	*dosC*	Globin sensor GGDEF	22
ydeH	b1535	P31129	*dgcZ*		CZB-GGDEF	23
yeaJ	b1786	P76237	*dgcJ*		GAPES1[c]-GGDEF	21
yeaP	b1794	P76245	*dgcP*		GAF-GGDEF	
yedQ	b1956	P76330	*dgcQ*		CHASE7[c]-xCache-GGDEF	21, 24, 25
yegE	b2067	P38097	*dgcE*		MASE1[b]-PAS-PAS-PAS-GGDEF-xEAL	12, 21, 26
yfiN	b2604	P46139	*dgcN*	*tpbB**	CHASE8[c]-HAMP-GGDEF	26–28
yliF	b0834	P75801	*dgcI*		GAPES2[c]-GGDEF	
yneF	b1522	P76147	*dgcF*		xMASE1-GGDEF	Promoter and first 4 TM segments deleted in *E. coli* K-12 (18)
EC55989_0813		B7LBD9	*dgcX*		MASE4[b]-GGDEF	Extra DGC in EAEC (18)
EcSMS35_1716		B1LFF9	*dgcY*		MASE5[b]-GGDEF	Extra DGC in *E. coli* SMS35 and NMEC 07:K1 strain CE10 (29)
Genes encoding c-di-GMP phosphodiesterases (intact EAL domains)						
rtn	b2176	P76446	*pdeN*		CSS[c]-EAL	
yahA	b0315	P21514	*pdeL*		LuxR-EAL	30, 31
ycgG	b1168	P75995	*pdeG*		CSS[c]-EAL	
yciR	b1285	P77334	*pdeR*	*gmr*	PAS-GGDEF-EAL	19, 20
yddU	b1489	P76129	*pdeO*	*dosP*	PAS-PAS-xGAF-xGGDEF-EAL	22, 30, 32, 33
yfeA	b2395	P23842	*pdeA*		MASE1[b]-xGGDEF-EAL	
yfgF	b2503	P77172	*pdeF*		MASE1[b]-xGGDEF-EAL	34, 35
yhjH	b3525	P37646	*pdeH*		EAL	21, 26, 36
yhjK	b3529	P37649	*pdeK*	*hmsP**	GAPES3[c]-HAMP-xGGDEF-EAL	
yjcC	b4061	P32701	*pdeC*		CSS[c]-EAL	
ylaB	b0457	P77473	*pdeB*		CSS[c]-EAL	
yliE	b0833	P75800	*pdeI*		CHASE9[c]-xCache-HAMP-xGGDEF-EAL	
yoaD	b1815	P76261	*pdeD*	*adrB*	CSS[c]-EAL	37
Z1528		Q8XAQ9	*pdeT*	*vmpA*	CSS[c]-EAL	Extra PDE in EHEC O157:H7 (18, 38)
EcE24377A_E0053		A7ZH68	*pdeW*		EAL	Extra PDE in ETEC E24377A (29)
ECP_2965		Q707K1	*pdeX*		EAL	Extra PDE in UPEC 536 (29)
UTI89_C1116		Q1RDG4	*pdeY*	*sfaY*	EAL	Extra PDE in several ExPEC strains (29, 39)
Genes encoding proteins with degenerate GGDEF and EAL domains						
ycgF	b1163	P75990	*bluF*		BLUF-xEAL	9, 40
yeaI	b1785	P76236	*cdgI*		MASE4[b]-xGGDEF	
ydiV	b1707	P76204	*rflP*		xEAL	Regulator of FlhDC proteolysis (10, 11)
yhdA	b3252	P13518	*csrD*		GAPES4[c]-xGGDEF-xEAL	8, 41

[a] The domain names indicate the following Pfam entries: BLUF, PF04940; Cache, PF02743; CHASE7, PF17151; CHASE8, PF17152; CHASE9, PF17153; CSS, PF12792; CZB, PF13682; EAL, PF00563; GAF, PF01590 or PF13492; GAPES1, PF17155; GAPES2, PF17156; GAPES3, PF17154; GAPES4, PF17157; GGDEF, PF00990; globin sensor, PF11563; HAMP, PF00672; LuxR, PF00196; MASE1, PF05231; MASE2, PF05230; MASE4, PF17158; MASE5, PF17178; PAS, PF08448 or PF13426. An "x" in front of a domain name indicates an enzymatically inactive or highly divergent domain. The Pfam entries for new sensor domains are to appear in the 29th release of the Pfam database (48).

[b] An integral membrane domain.

[c] Predicted periplasmic domain.

[d] Asterisks indicate designations used for homologous genes in other genera or species as follows: *adrA*, *Salmonella* (occasionally, *adrA* has also been used for *E. coli*); *tpbB*, *Pseudomonas aeruginosa*; *hmsP*, *Yersinia*.

[e] ETEC, enterotoxigenic *E. coli*; ExPEC, extraintestinal pathogenic *E. coli*; NMEC, neonatal meningitis *E. coli*; EAEC, enteraggregative *E. coli*; TM, transmembrane.

K-12 *E. coli* strains had to be given names, and it seemed obvious to use a *dgc* and *pde* nomenclature (29).

Therefore, as a group of researchers who in recent years have worked on the molecular mechanisms and/or the genomic basis of c-di-GMP signaling in *E. coli*, we now propose a general and systematic *dgc* and *pde* nomenclature for the enzymatically active GGDEF/EAL domain-encoding genes of *E. coli* (Table 1). By using these self-explanatory designations, we also reflect a trend for similar (though not yet systematically used) names for GGDEF/EAL domain proteins in some other species, including *Caulobacter*, *Pseudomonas*, *Listeria*, and *Bdellovibrio* spp. We are fully aware that nomenclature is a convention and sometimes has to include oversimplifications (for instance, for proteins with multiple functions), but its main function is to allow researchers to remember things and communicate more easily. In detail, the proposed nomenclature is based on the following considerations.

- Following the principle that genes should be named according to the molecular function of the gene product and not according to a mutant phenotype that may be due to a very indirect connection and may represent a functional side effect, "*dgc*" and "*pde*" designations are based either on experimentally determined DGC and PDE activities or on the presence of the conserved key amino acids required for these enzymatic functions. These conserved amino acids include the (G/A/S)G(D/E)EF motif in DGCs (43, 44) and the presence of the catalytic glutamyl residue and the main amino acids involved in c-di-GMP and cation binding in PDEs (45–47). The latter criterion reflects pragmatic reasons of feasibility—while isolated and usually soluble EAL domains alone often show PDE activity *in vitro*, isolated GGDEF domains are usually inactive, which makes measuring DGC activity of membrane-associated DGCs rather challenging. Not only should sensory input domains be integrated into an appropriately reconstituted lipid environment to allow dimerization of the GGDEF domains as a prerequisite for enzymatic activity, but these sensory domains might also need to bind as-yet-unknown ligands in order to promote enzymatic activity.
- The seven composite proteins with both GGDEF and EAL domains can be unequivocally assigned DGC or PDE functions and therefore the corresponding gene designations. In six of the seven cases, one of the two domains is clearly degenerate (Table 1). Only YciR features intact GGDEF and EAL domains, but it has been demonstrated that, in this case, the purified protein shows strong PDE activity *in vitro* (19, 20), whereas its GGDEF domain binds GTP but has only very minor and, in fact, cryptic DGC activity (20). We therefore propose *pdeR* as a new gene designation for *yciR*, with the "R" also seeming appropriate because PdeR is the core component of a regulatory switch that controls the expression of the CsgD major biofilm regulator in *E. coli*. Thus, PdeR is a multifunctional "trigger protein," whose ability to bind and degrade c-di-GMP plays a regulatory role as it modulates the direct inhibitory interactions of PdeR with the transcription factor complex that controls *csgD* expression (20).
- In order to make the transition to the systematic nomenclature easier for people who have been working with these genes and proteins of *E. coli*, we propose to retain the capital letter currently found in the *y* designations (e.g., *ydaM* becoming *dgcM*, etc.) in as many cases as possible. There is only a single case of overlap—we suggest that *yfeA* should be renamed *pdeA* but that *yahA* should be renamed *pdeL* (referring to its N-terminal LuxR domain). In the case of *ydeH*, *dgcZ*, which alludes to the zinc binding of the sensory domain of the gene product, has already been introduced (23).
- In the few cases where genes are in operons, we propose to use the same capital letter; i.e., we propose that *yliF* and *yliE* should become *dgcI* and *pdeI* and that *ycdT* and a *pde* gene that follows *ycdT* in certain EHEC strains should become *dgcT* and *pdeT*.
- For a few already renamed genes (e.g., genes *dosC* and *dosP* and genes *vmpA* and *sfaY*), we suggest retaining these names as alternative designations but also reserving systematic names (e.g., genes *dgcO* and *pdeO* and genes *pdeT* and *pdeY*, respectively) and leaving it to the researchers working with these genes to determine which designation they want to use (for clarity, we suggest also mentioning the other designations in future publications). In addition, Table 1 also includes a few established designations for corresponding homologs in other bacterial species.
- Among the four genes encoding proteins with degenerate GGDEF/EAL domains only, *yeaI* is the only one that encodes a protein that binds c-di-GMP (F. Skopp and R. Hengge, unpublished data), indicating that this protein serves as a c-di-GMP-binding effector. We therefore propose *cdgI* as a new designation. For the other three genes, which encode proteins that do not bind c-di-GMP, we suggest that the previously assigned designations that reflect the functions of the encoded proteins should be retained. Thus, *ycgF* was already renamed *bluF* (alluding to its blue-light sensing BLUF domain) (9, 40) and *yhdA* was renamed *csrD* (as it controls the CsrA/CsrB/CsrC system) (8). Degenerate EAL-only protein YdiV was shown to directly inhibit and promote proteolysis of the flagellar master regulator FlhDC (10, 11), and we therefore propose *rflP* (regulator of FlhDC proteolysis) as a new gene name.

Besides assigning new systematic names to the genes and proteins involved in c-di-GMP signaling in *E. coli*, we also use this opportunity to introduce systematic designations for several N-terminal sensory input domains present in some of these proteins that have not been described before (Table 1). In particular, these are (i) two novel MASE (membrane-associated sensor) domains, i.e., MASE4, an eight-transmembrane helix domain found in DgcX and DgcT (YcdT) and the degenerate c-di-GMP-binding protein CdgI (YeaI) (18, 29), and MASE5, a six-transmembrane helix domain present in DgcY (29); (ii) four distinct "GAPES" domains (referring to gammaproteobacterial periplasmic sensory domains), which occur in DgcJ (YeaJ), DgcI (YliF), PdeK (YhjK), and CsrD; and (iii) three novel CHASE (cyclases/histidine kinase-associated sensory) domains present in DgcQ (YedQ), DgcN (YfiN), and PdeI (YliE). In contrast to CHASE domains, GAPES domains seem to be restricted to GGDEF/EAL domain proteins. The molecular functions in c-di-GMP signaling of all of these sensory input domains have yet to be elucidated.

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