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Definitive Nomenclature of GES/IBC-Type Extended-Spectrum β-Lactamases

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Abstract Because there are no unified nomenclature systems for either GES-type or IBC-type extended-spectrum β-lactamases (ESBLs), we propose a unified and definitive nomenclature system for GES/IBC-type ESBLs. This proposed nomenclature update is greatly helpful in two points: (i) it would not confuse microbiologists studying GES-type ESBLs, fundamentally preventing misleading nomenclature of these antibiotic resistance genes, and (ii) the definitive renaming of GES/IBC-type ESBLs can help some researchers to correctly designate new GES-type ESBLs such as novel enzymes identified from some nationwide surveys.

Key words: Nomenclature, extended-spectrum β-lactamase, GES-type, IBC-type

The β-lactamases produced by bacteria are known to protect against the lethal effect of penicillins, cephalosporins, carbapenems, or monobactams on cell-wall synthesis. The production of β-lactamase is the single most prevalent mechanism responsible for resistance to β-lactams among clinical isolates of *Pseudomonas aeruginosa* and the family *Enterobacteriaceae*, and thus, pose therapeutic problems [3, 10, 11, 23, 25]. The Antimicrobial Availability Task Force (AATF) of the Infectious Diseases Society of America (IDSA) reported ESBL (extended-spectrum beta-lactamases)-producing *Enterobacteriaceae* as a bacterium of particularly problematic pathogens [6]. ESBLs are clavulanate-susceptible enzymes conferring broad resistance to penicillins, aztreonam, and cephalosporins (with the exception of cephamycins) [15]. ESBLs are often plasmid mediated, and most of them are mutants of the classic TEM and SHV enzymes, with one or more amino-acid substitutions around the active site [19]. These changes allow hydrolysis of extended-spectrum cephalosporins (*e.g.*, ceftazidime and cefotaxime) and monobactams (*e.g.*, aztreonam), which are stable to classic TEM and SHV enzymes [1]. There are also reports of clinical isolates of *Enterobacteriaceae* producing various non-TEM, non-SHV ESBLs: CTX-M and GES/IBC-types [1, 13]. In particular, GES/IBC-type ESBLs is greatly problematic because these ESBLs can be non-metallo-carbapenemases hydrolyzing carbapenems (*e.g.*, imipenem and meropenem), which have the broadest activity spectra of any β-lactam antibiotics and are often the most appropriate agents for use in the treatment of infections caused by multiresistant Gram-negative aerobic bacteria [14]. Therefore, typing of GES/IBC-type ESBLs is very important for studying the epidemiology and prevalence of carbapenem-hydrolyzing and ESBL-producing pathogens.

The exact nomenclature systems of GES/IBC-type ESBLs are also necessary for the typing of these ESBLs and can also help some researchers to correctly designate new GES-type ESBLs, such as novel enzymes identified from some nationwide surveys. However, in three recently published articles [9, 12, 22], the nomenclature systems of GES-type ESBLs still cause confusion because there are no final decisions concerning the nomenclature system suggested by Lee *et al.* [12]. Furthermore, there are no unified nomenclature systems for either GES-type (Guiana-Extended-Spectrum β-lactamase) or IBC-type (Integron-Borne Cephalosporinase) ESBLs, although IBC-types are just point mutant analogs of GES-types.

Because different GES-type ESBLs that possess different hydrolytic properties have previously been designated with identical names (Table 1), Lee *et al.* [12] suggested that according to the release order of relevant sequences into the public domain, the GES genes described by Vourli *et al.* [26] be maintained as GES-3 and GES-4, respectively,

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Table 1. Nomenclature, epidemiology, and amino-acid differences of GES/IBC-type ESBLs.

Designation	GenBank accession number	Country of origin	Isolated from other countries	Clinical isolates	Amino-acid (coding triplet) differences at Ambler's position[a]:					References
					62	104	125	170	243	
GES-1	AF156486	French Guiana	Brazil, Portugal, Argentina, South Africa	*K. pneumoniae* *P. aeruginosa*	Met (ATG)	Glu (GAA)	Ala (GCT)	Gly (GGC)	Gly (GGC)	2, 4, 5, 17, 21, 29
GES-2	AF326355	South Africa	Argentina	*P. aeruginosa*				Asn (AAC)		18, 20
GES-3	AB113580	Japan		*K. pneumoniae*	Thr (ACG)	Lys (AAA)				28
GES-4	AB116260	Japan		*K. pneumoniae*	Thr (ACG)	Lys (AAA)		Ser (AGC)		27
GES-5[b]	AY494717	Greece	Korea	*E. coli* *K. pneumoniae*				Ser (AGC)		9, 24, 27
GES-6[c]	AY494718	Greece		*K. pneumoniae*		Lys (AAA)		Ser (AGC)		26
GES-7 (IBC-1)	AF208529	Greece		*E. cloacae*		Lys (AAA)				7
GES-8 (IBC-2)	AF329699	Greece		*P. aeruginosa*			Leu (CTG)			16
GES-9	AY920928	France		*P. aeruginosa*					Ser (AGC)	22

[a]Amino-acid residue and coding triplet differences are depicted in relation to GES-1.
[b]GES-type ESBL previously designated GES-3.
[c]GES-type ESBL previously designated GES-4.

whereas those described by Wachino *et al.* [27, 28] should be renamed as GES-5 and GES-6, respectively. To the suggestion of Lee *et al.* [12], Wachino and Arakawa replied that they submitted their sequence data for GES-3 and GES-4 to the GenBank/EMBL/DDBJ earlier than Vourli *et al.* Moreover, their manuscripts have been submitted to the American Society for Microbiology earlier than the manuscript (submitted to the Federation of European Microbiological Societies) of Vourli *et al.* [12: Authors' Reply 1]. In Authors' Reply 2 [12], Poirel and Nordmann proposed to maintain the current denomination concerning the fully characterized GES-3 and GES-4 enzymes reported by Wachino *et al.* and to rename the variants (GES-3 and GES-4) reported by Vourli *et al.* as GES-5 and GES-6, respectively. Lee's research group agreed with the suggestions made by the two Author's groups, although Lee's group could not state that point in the article [12]. Thus, Jeong *et al.* (Lee's research group) [9] renamed the variants (GES-3 and GES-4) reported by Vourli *et al.* as GES-5 and GES-6, respectively, and stated that the GES-5 gene that has broken out in Korea differed by just one silent mutation (G→A) at position 54 from the variant (GenBank accession no. AY494717) reported by Vourli *et al.* However, in the recent article of Poirel *et al.* [22], they proposed to rename the variants reported by Wachino *et al.* as GES-5 and GES-6 (for GES-3 and GES-4, respectively), citing the nomenclature update first proposed by Lee *et al.* [12].

These contrary mentionings on the nomenclature of GES-type ESBLs were a result of the absence of the final decision on the nomenclature update proposed by Lee *et al.* [12]. Furthermore, IBC-1 and IBC-2 differ by only one amino acid residue from GES-1 [7, 16]. Thus, a unified and definitive nomenclature system including both GES- and IBC-type ESBLs is needed. To clarify the misleading nomenclature of GES/IBC-type ESBLs, we propose to rename the variants (GES-3 and GES-4) reported by Vourli *et al.* as GES-5 and GES-6, respectively, and the IBC-1 and IBC-2 variants identified in Greece [7, 16] as GES-7 and GES-8, respectively (Table 1). Table 1 includes nine currently known variants from GES-1 to GES-9 and exhibits their epidemiology.

To fundamentally prevent misleading nomenclature of these antibiotic resistance genes, it is crucial to develop a central Web site with bioinformatics capabilities to serve as a repository for all sequences and name designations for genes encoding antibiotic resistance [8]. There is currently only a β-lactamase Web site (http://www.lahey.org/studies/webt.asp) whereby sequences, literature references, or database accession numbers for most β-lactamase families are posted and numbers are assigned. Whether this system succeeds or not depends on the cooperation of each researcher and the voluntary participation by the keepers of the Web site. Prior to our present report, the information on the Web site still reflected inconsistencies regarding

denominations of GES-3 to GES-8. The repository data have since been changed to be in keeping with our unified and definitive nomenclature system including GES/IBC-type ESBLs (George Jacoby, personal communication). It is with this background that we propose a unified and definitive nomenclature system for GES/IBC-type ESBLs, as set out in Table 1.

In conclusion, this proposed nomenclature update would not confuse microbiologists studying GES-type ESBLs, fundamentally preventing misleading nomenclature of these antibiotic resistance genes. The definitive renaming of GES/IBC-type ESBLs can also help some researchers to correctly designate new GES-type ESBLs, such as novel enzymes identified from some nationwide surveys.

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