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Updated Sequence Information for TEM β-Lactamase Genes

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The sequences of the promoter regions and of the structural genes for 13 penicillinase, extended-spectrum, and inhibitor-resistant TEM-type β-lactamases have been determined, and an updated bla_{TEM} gene nomenclature is proposed.

In members of the family *Enterobacteriaceae*, the most prevalent mechanism of resistance to broad-spectrum β-lactams is detoxification of the drugs by plasmid-mediated enzymes that are variants of TEM and SHV penicillinases (4, 13). The TEM-derived extended-spectrum or inhibitor-resistant β-lactamases differ from the parental TEM-1 and TEM-2 penicillinases by various combinations of amino acid substitutions. The structural genes for TEM-1 penicillinases are designated bla_{TEM-1a} and bla_{TEM-1b}, and the structural gene for TEM-2 is designated bla_{TEM-2} (10). As an aid to the study of the mutational events which account for the sequence diversity of TEM-type β-lactamases and to the nomenclature of the numerous variants, we have determined and analyzed the sequences of the structural genes and of the promoters of various bla_{TEM} genes. Amplification and direct sequencing of the PCR product were as described previously (15). The origins (Table 1) and the nucleotide changes in the bla_{TEM} genes and the corresponding amino acid substitutions in the deduced sequence of the enzymes (Tables 2 and 3) are summarized.

Two promoters for initiation of transcription of the bla_{TEM} genes have been described: the weak *P3* promoter for bla_{TEM-1} in Tn*3* (20) and, following a C-to-T substitution at position 32, the two overlapping promoters (*Pa* and *Pb*) which lead to a ca. 10-fold increase in transcriptional levels (8).

Penicillinases. (i) bla_{TEM-1c}. *Escherichia coli* BM2729 was isolated in 1989 and has a phenotype of resistance to β-lactam antibiotics which corresponds to the synthesis of a penicillinase. The corresponding bla_{TEM-1c} gene differs from bla_{TEM-1a} by the nucleotide substitution C_{436}→T, which is silent.

(ii) bla_{TEM-13}. *Morganella morganii* BM2717 (14) harbored a plasmid that carries both the bla_{TEM-2} and the bla_{TEM-13} genes (data not shown). The sequence of bla_{TEM-13} differs from that of bla_{TEM-2} by C_{990}→T, resulting in Thr_{265}→Met, as determined by oligotyping (14). Most interestingly, upstream from bla_{TEM-13} and bla_{TEM-2} we found the weak promoter *P3* (C_{32}) instead of the expected strong promoters *Pa* and *Pb*. The presence of the two genes on the same replicon could therefore result from gene duplication followed by a point mutation.

Extended-spectrum β-lactamases. (i) bla_{TEM-8}. The TEM-8 extended-spectrum β-lactamase, later designated CAZ-2 (6), was detected in *Klebsiella pneumoniae* HM12, which was isolated in 1987, and the structural gene for the enzyme was sequenced (6, 17). The promoter region has a thymine at position 32 (Table 2) which was not reported for the gene for CAZ-2. The bla_{TEM-8} gene derives from bla_{TEM-2} by three base pair changes and differs from bla_{TEM-3} at position 692, where a C-to-A substitution leads to Arg_{164}→Ser.

(ii) bla_{TEM-11}. The gene for the extended-spectrum β-lactamase TEM-11 harbored by *E. coli* 1724A (27) was oligotyped (14), with a remaining ambiguity found at position 238, and was characterized by restriction fragment length polymorphism analysis, which revealed an adenine at position 925 (2). However, sequence determination indicated G_{925} (Table 2). Thus, the bla_{TEM-11} gene differs from bla_{TEM-2} at two positions, G_{693}→A, resulting in Arg_{164}→His, and A_{925}→G, which is silent. The strong promoters *Pa* and *Pb* for that gene are identical to those for bla_{TEM-2}. The bla_{TEM-11} gene could therefore result from a recombination event, in the vicinity of position 692, between bla_{TEM-2}, which would have provided the 5′ portion of the gene, and bla_{TEM-6} (11), which would have contributed the 3′ part of the gene. Alternatively, the bla_{TEM-11} gene could be a point mutant from a yet uncharacterized TEM-2 progenitor with a G_{925} or a double mutant of bla_{TEM-2}.

(iii) $bla_{TEM-15a}$. The gene for extended-spectrum β-lactamase TEM-15 from *K. pneumoniae* BM2730 was oligotyped (14) and was sequenced without the promoter (21). We have resequenced the entire region whose sequence differs from that of bla_{TEM-1a} at three positions: G_{512}→A (Glu_{104}→Lys), G_{914}→A (Gly_{238}→Ser), and G_{162}→T. The last change occurs at position 1 of the −10 consensus Pribnow box sequence of the *P3* promoter and has been shown to be responsible for the hyperproduction of TEM-1 (22). We suggest the designation *P4* for this new promoter. Since this structural gene was apparently derived from bla_{TEM-1a}, we propose the nomenclature $bla_{TEM-15a}$.

(iv) $bla_{TEM-15b}$. The deduced amino acid sequence of $bla_{TEM-15b}$ is identical to that of $bla_{TEM-15a}$. The enzyme, formerly designated TEM-17 on the basis of oligotyping (14), was therefore redesignated TEM-15. The TEM-17 sequence that we originally proposed has subsequently been found in *Capnocytophaga ochracea* (EMBL accession no. Y14574). The sequence of $bla_{TEM-15b}$ differs from that of bla_{TEM-1b} at two positions: G_{512}→A, which leads to Glu_{104}→Lys, and G_{914}→A, which results in Gly_{238}→Ser, whereas the strong *Pa* and *Pb* promoters are present upstream. We thus suggest the designation $bla_{TEM-15b}$ since this gene is likely to be derived from bla_{TEM-1b}. The TEM-15 β-lactamase displays the same amino acid substitutions which enlarge the substrate range of TEM-3, except that TEM-15 has Gln_{39} instead of Lys.

(v) $bla_{TEM-12c}$ and $bla_{TEM-10b}$. $bla_{TEM-12c}$ and $bla_{TEM-10b}$ originate from two *E. coli* strains, F1 and F2, which were isolated from the same patient at a 24-h interval (26). The $bla_{TEM-12c}$ gene is identical to bla_{TEM-12}, which encodes YOU-2 (19), and is located downstream from the *Pa* and *Pb* promoters. Since $bla_{TEM-12a}$ refers to the structural gene for TEM-101 (9) and $bla_{TEM-12b}$ is the designation for the gene

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TABLE 1. Origins of the enzymes studied

Enzyme	Alternate designation(s)	Gene(s)	Clinical isolate(s)	Origin or reference
TEM-1		bla_{TEM-1c}	*E. coli* BM2729	This work
TEM-8	CAZ-2	bla_{TEM-8}	*K. pneumoniae* HM12	14, 17
TEM-10	TEM-23, MGH-1	$bla_{TEM-10b}$ and bla_{TEM-23}	*E. coli* F2	26
TEM-11	CAZ-lo	bla_{TEM-11}	*E. coli* 1724A	14, 27
TEM-12	TEM-101, YOU-2, CAZ-3	$bla_{TEM-12c}$	*E. coli* F1, *E. coli* MG32	26, 28
TEM-13		bla_{TEM-13}	*M. morganii* BM2717	14
TEM-15		$bla_{TEM-15a}$	*K. pneumoniae* BM2730	14
TEM-15	TEM-17	$bla_{TEM-15b}$	*K. pneumoniae* BM2731 and BM2732	14
TEM-24	CAZ-6	$bla_{TEM-24b}$	*E. aerogenes* SLE48	This work
TEM-53		bla_{TEM-53}	*K. pneumoniae* BM2733	This work
TEM-33	IRT-5	$bla_{TEM-33b}$	*E. coli* BM2725	This work
TEM-33	IRT-5	$bla_{TEM-33c}$	*E. coli* BM2724	This work
TEM-54		bla_{TEM-54}	*E. coli* BM2728	This work

described by Heritage et al. (12) and also the gene for CAZ-3 (7), we propose the nomenclature $bla_{TEM-12c}$. We also found a $bla_{TEM-12c}$ gene in *E. coli* MG32 (28). This gene was chromosomally located and, in an unusual fashion, was preceded by the weak *P3* promoter.

The sequence of $bla_{TEM-10b}$ differs from that of $bla_{TEM-12c}$ by a single base pair change, $G_{917}\rightarrow A$, which results in $Glu_{240}\rightarrow Lys$. The $bla_{TEM-10b}$ gene is identical to bla_{TEM-10} from plasmids pJPQ100 and pMG223 in *K. pneumoniae* and pCLL2302 in *E. coli* (18, 19). These genes could be designated $bla_{TEM-10b}$ since they are derived from bla_{TEM-1b}; $bla_{TEM-10a}$ would then correspond to the gene carried by pCLL2301 from *K. pneumoniae* (18), which is derived from bla_{TEM-1a}. The structural genes for TEM-10 and TEM-12 have previously been detected in the same clinical isolate (3).

(vi) $bla_{TEM-24b}$. The sequence of bla_{TEM-24} encoding TEM-24 (or CAZ-6) has been published with only part of the promoter region (6), and we suggest the designation $bla_{TEM-24a}$. The sequence of $bla_{TEM-24b}$ differs by a silent mutation ($T_{682}\rightarrow C$) from that of $bla_{TEM-24a}$ and is under the control of the strong promoters *Pa* and *Pb*. It has been proposed that $bla_{TEM-24a}$ could result from recombination of bla_{TEM-3} and bla_{TEM-5} between positions 604 and 682 (6). Similarly, $bla_{TEM-24b}$ could originate from a recombination event between positions 693 and 911 of bla_{TEM-8} (6, 17) and bla_{TEM-5} (23). Whatever the authentic origin of the gene may be, our observation documents dissemination of TEM-24 in *Enterobacter aerogenes*.

(vii) bla_{TEM-53}. The sequence of the new mutant gene bla_{TEM-53} differs from that of bla_{TEM-2} at three loci, with each base pair change leading to an amino acid substitution: $C_{263}\rightarrow T$ ($Leu_{21}\rightarrow Phe$), $A_{317}\rightarrow C$ ($Lys_{39}\rightarrow Gln$), and $C_{692}\rightarrow A$ ($Arg_{164}\rightarrow Ser$). The gene is expressed from the strong promoters *Pa* and *Pb*. It is worth noting that the corresponding mature

TABLE 2. Substitutions in bla_{TEM} genes and derived penicillinases and extended-spectrum β-lactamases

Region and nucleotide no.[a] (amino acid no.[b])	Nucleotide (amino acid) in the following gene (enzyme):					
	bla_{TEM-1a} (TEM-1 [Tn*3*])	bla_{TEM-1b} (TEM-1 [Tn*2*])	bla_{TEM-2} (TEM-2 [Tn*1*])	bla_{TEM-1c} (TEM-1)	bla_{TEM-8} (TEM-8)	$bla_{TEM-10b}$ (TEM-10)
Promoter region	*P3*	*P3*	*Pa* and *Pb*	*P3*	*Pa* and *Pb*	*Pa* and *Pb*
32	C	C	T	C	T	T
147	T	T	T	T	A	T
162	G	G	G	G	G	G
175	A	G	A	A	A	G
Coding region						
226[d]	C (Phe)	T	C	C	C	T
263 (21)	C (Leu)[21]	C	C	C	C	C
317 (39)	C (Gln)[39]	C (Gln)[39]	A (Lys)[39]	C (Gln)[39]	A (Lys)[39]	C (Gln)[39]
346[d]	A (Glu)	A	G	A	G	A
436[d]	C (Gly)	T	T	T	T	T
512 (104)	G (Glu)[104]	G	G	G	A (Lys)[104]	G
604[d]	G (Ala)	T	G	G	G	T
682[d]	T (Thr)	T	C	T	C	T
692 (164)	C (Arg)[164]	C	C	C	A (Ser)[164]	A (Ser)[164]
693 (164)	G (Arg)[164]	G	G	G	G	G
911 (237)	G (Ala)[237]	G	G	G	G	G
914 (238)	G (Gly)[238]	G	G	G	A (Ser)[238]	G
917 (240)	G (Glu)[240]	G	G	G	G	A (Lys)[240]
925[d]	G (Gly)	G	A	G	A	G
990 (265)	C (Thr)[265]	C	C	C	C	C

[a] Numbering is according to Sutcliffe (25).
[b] Numbering is according to Ambler et al. (1).
[c] Position 32 is T for $bla_{TEM-12c}$ from *E. coli* F1 (26) and C for $bla_{TEM-12c}$ from *E. coli* MG32 (28).
[d] Position at which only silent mutations occur.

TABLE 3. Substitutions in bla_{TEM} genes and derived inhibitor-resistant β-lactamases

Region and nucleotide no.[a] (amino acid no.[b])	Nucleotide (amino acid) in the following gene (enzyme):					
	bla_{TEM-1a} (TEM-1 [Tn*3*])	bla_{TEM-1b} (TEM-1 [Tn*2*])	bla_{TEM-2} (TEM-2 [Tn*1*])	$bla_{TEM-33b}$ (TEM-33)	$bla_{TEM-33c}$ (TEM-33)	bla_{TEM-54} (TEM-54)
Promoter region	*P3*	*P3*	*Pa* and *Pb*	*Pa* and *Pb*	*P4*	*Pa* and *Pb*
32	C	C	T	T	C	T
162	G	G	G	G	T	G
175	A	G	A	G	A	A
Coding region						
226[c]	C (Phe)	T	C	T	C	C
317 (39)	C (Gln)[39]	C (Gln)[39]	A (Lys)[39]	C (Gln)[39]	C (Gln)[39]	C (Gln)[39]
346[c]	A (Glu)	A	G	A	G	A
407 (69)	A (Met)[69]	A	A	C (Leu)[69]	C (Leu)[69]	A
436[c]	C (Gly)	T	T	T	T	C
604[c]	G (Ala)	T	G	T	G	G
682[c]	T (Thr)	T	C	T	C	T
925[c]	G (Gly)	G	A	G	A	G
929 (244)	C (Arg)[244]	C	C	C	C	C
930 (244)	G (Arg)[244]	G	G	G	G	T (Leu)[244]
1022 (276)	A (Asn)[276]	A	A	A	A	A

[a] Numbering is according to Sutcliffe (25).
[b] Numbering is according to Ambler et al. (1).
[c] Positions at which only silent mutations occur.

protein is identical to TEM-12. This gene could be secondary to a recombination event, between positions 436 and 512, of bla_{TEM-4} (23) or bla_{TEM-9} (16), which would provide the 5′ third of the gene, and bla_{TEM-7} (9), which would correspond to the 3′ two-thirds.

Inhibitor-resistant β-lactamases. (i) bla_{TEM-33}. The sequence of bla_{TEM-33}, which we propose be renamed $bla_{TEM-33a}$, has been published (24). We report here the sequence of two genes, designated $bla_{TEM-33b}$ and $bla_{TEM-33c}$, that have been detected in clinical isolates (Table 1).

(ii) $bla_{TEM-33b}$. The structural gene has the mutation $A_{407}\rightarrow C$ relative to the sequence of bla_{TEM-1b}, resulting in $Met_{69}\rightarrow Leu$, and is under the control of the *Pa* and *Pb* promoters.

(iii) $bla_{TEM-33c}$. $bla_{TEM-33c}$ is derived from bla_{TEM-2} following two changes: $A_{317}\rightarrow C$ ($Lys_{39}\rightarrow Gln$) and $A_{407}\rightarrow C$

TABLE 2—*Continued*

Nucleotide (amino acid) in the following gene (enzyme):						
bla_{TEM-11} (TEM-11)	$bla_{TEM-12c}$ (TEM-12)	bla_{TEM-13} (TEM-13)	$bla_{TEM-15a}$ (TEM-15)	$bla_{TEM-15b}$ (TEM-15)	$bla_{TEM-24b}$ (TEM-24)	bla_{TEM-53} (TEM-53)
Pa and *Pb*	*Pa* and *Pb* or *P3*	*P3*	*P4*	*Pa* and *Pb*	*Pa* and *Pb*	*Pa* and *Pb*
T	T/C[c]	C	C	T	T	T
T	T	T	T	T	A	T
G	G	G	T	G	G	G
A	G	A	A	G	A	A
C	T	C	C	T	C	C
C	C	C	C	C	C	T (Phe)[21]
A (Lys)[39]	C (Gln)[39]	A (Lys)[39]	C (Gln)[39]	C (Gln)[39]	A (Lys)[39]	C (Gln)[39]
G	A	G	A	A	G	G
T	T	T	C	T	T	T
G	G	G	A (Lys)[104]	A (Lys)[104]	A (Lys)[104]	G
G	T	G	G	T	G	G
C	T	C	T	T	C	C
C	A (Ser)[164]	C	C	C	A (Ser)[164]	A (Ser)[164]
A (His)[164]	G	G	G	G	G	G
G	G	G	G	G	A (Thr)[237]	G
G	G	G	A (Ser)[238]	A (Ser)[238]	G	G
G	G	G	G	G	A (Lys)[240]	G
G	G	A	G	G	G	A
C	C	T (Met)[265]	C	C	C	C

(Met_{69}→Leu). The promoter region has the G_{162}→T mutation, which is commonly found upstream from the genes for inhibitor-resistant β-lactamases. Thus, the $bla_{TEM\text{-}33c}$ gene is derived from that for the "TEM-2 like" enzyme (5), which consists of TEM-2 with Lys_{39}→Gln and the T_{32}→C and G_{162}→T mutations upstream from the gene.

(iv) $bla_{TEM\text{-}54}$. $bla_{TEM\text{-}54}$ has not yet been described and originates from *E. coli* BM2728 (Table 1). It derives from $bla_{TEM\text{-}1a}$ following one mutation, G_{930}→T, which leads to the amino acid change Arg_{244}→Leu, whereas the promoter region corresponds to *Pa* and *Pb*.

In summary, we have determined the sequences of the structural genes and of the promoter regions specifying two TEM-derived penicillinases, eight extended-spectrum β-lactamases, and three inhibitor-resistant β-lactamases. The sequence variety found probably reflects the existence in nature of genes other than $bla_{TEM\text{-}1a}$, $bla_{TEM\text{-}1b}$, $bla_{TEM\text{-}1c}$, $bla_{TEM\text{-}2}$, and $bla_{TEM\text{-}13}$ for penicillinases. With the exception of chromosomal $bla_{TEM\text{-}12}$, the genes were located downstream from strong promoters such as *Pa* and *Pb* and the new promoter *P4*.

Nucleotide sequence accession numbers. The nucleotide sequence data for $bla_{TEM\text{-}53}$ and $bla_{TEM\text{-}54}$ have been submitted to the GenBank nucleotide sequence data library under accession no. AF104441 and AF104442, respectively.

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