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Compilation and alignment of DNA polymerase sequences

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INTRODUCTION

More than 40 different DNA polymerases, including some putative DNA polymerase sequences deduced from nucleotide sequence data, have recently been reported (1–39). The amino acid sequences of these DNA polymerases have been aligned and partial homologous regions identified by many investigators (2–4,9,10,12–25,27–36,42–51). Based on the segmental amino acid sequence similarities, DNA polymerases have been classified into two major groups; *E. coli* DNA polymerase I-Type and eukaryotic DNA polymerase α-Type (14,44,47,48,51), or family A DNA polymerases and family B DNA polymerases (4,9,50). As the number of DNA polymerase sequences increases, the classification of DNA polymerases becomes increasingly ambiguous. For example, DNA polymerase delta of yeast was shown to have amino acid sequence similarity to the α-Type DNA polymerases (17). It has become necessary to establish a unified classification of DNA polymerases. Here we propose to classify DNA polymerases into families A, B, and C (Figure 1: A, B, and C), according to the amino acid sequence homologies with *E. coli* DNA polymerases I, II, and III, respectively. As new and different prokaryotic and eukaryotic DNA polymerases are identified, the number of families can easily be expanded by using additional letters of the alphabet (i.e., D, E, etc.).

The bacterium *E. coli* (strain K12) contains three distinct DNA polymerases I, II, and III (52). *E. coli* DNA polymerase I, the first DNA polymerase discovered, is specified by the *pol*A gene (52). *E. coli* DNA polymerase II, encoded by the *pol*B gene, was recently sequenced and found to be identical to the *din*A gene, a DNA damage inducible gene whose expression is regulated by the SOS system in *E. coli* (8,53). Amino acid sequence alignment shows that *E. coli* DNA polymerase II has significant homology with family B (α-Type) DNA polymerases (8,53,54).

E. coli DNA polymerase III is a multisubunit enzyme encoded by various *dna* genes (55); the DNA polymerizing α-subunit encoded by the *pol*C (*dna*E) gene (56) and the 3′→5′ exonuclease performing ε-subunit encoded by the *dna*Q gene (57). The α-subunit of *E. coli* DNA polymerase III exhibits an extensive homology with the corresponding α-subunit of *Salmonella typhimurium* DNA polymerase III (35); and both show significant homology to *Bacillus subtilis* DNA polymerase III, a single-polypeptide encoded by the *pol*C gene (36).

In summary, family A DNA polymerases are named for their homology to the product of the *pol*A gene encoding *E. coli* DNA polymerase I; family B DNA polymerases are named for their homology to the product of the *pol*B gene encoding *E. coli* DNA polymerase II; and family C DNA polymerases are named for their homology to the product of the *pol*C gene encoding *E. coli* DNA polymerase III.

The eukaryotic DNA polymerase β, the smallest known DNA polymerase, does not have homology with those of any of the DNA polymerase families described above. Instead, DNA polymerase β has homology with terminal transferases (37). This β group we will call family X (Figure 1D). The classification and original reference(s) for the amino acid sequences of each DNA polymerase are shown in Table 1.

All of the family A DNA polymerases, except for yeast mitochondrial DNA polymerase I, are prokaryotic and are very sensitive to dideoxynucleotide inhibitors, and therefore are useful enzymes for DNA sequencing by the chain-termination method (58). The family A DNA polymerases are resistant to aphidicolin. The family B DNA polymerases are quite extensive in number and variety. Most of the family B DNA polymerases, if not all, are sensitive to aphidicolin and relatively resistant to dideoxynucleotide inhibitors. Most of the family B DNA polymerases, except for pAI2 (33) and yeast DNA polymerase II (16), contain the highly conserved amino acid sequence motif **YGDTD**, which has been suggested to form part of the dNTP binding site. Amino acid substitutions in this conserved sequence resulted in defects in the DNA polymerase activity without affecting the 3′→5′ exonuclease activity (59,60,61). The family C DNA polymerases are major bacterial replicative DNA polymerases which do not have appreciable homology with those of family A and B DNA polymerases. *B. subtilis* DNA polymerase III is a single polypeptide that is highly sensitive to hydroxyphenylazouracil (62). It is anticipated that the number of sequenced family C DNA polymerases will increase rapidly, since all of the aerobic bacteria may contain a member of this family of DNA polymerases.

SEQUENCE ALIGNMENT

The **37** complete DNA polymerase sequences and 3 complete terminal deoxynucleotidyltransferase (TDT) sequences are listed in 4 groups; the fa
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SEQUENCE ALIGNMENT

The **37** complete DNA polymerase sequences and 3 complete terminal deoxynucleotidyltransferase (TDT) sequences are listed in 4 groups; the family A DNA polymerases, the family B DNA polymerases, the family C DNA polymerases, and family X DNA polymerases (including TDTs). In order to limit the space needed for the alignment, we omitted DNA polymerase sequences that are very similar to the prototype DNA polymerase. The DNA polymerases not shown include: herpes virus type-2 (63),

adenovirus type-5 (64), bacteriophage T3 (65), and bacteriophage PZA (66).

ACCURACY OF SEQUENCE DATA

Whenever a sequence ambiguity existed in a published sequence, we contacted the authors to obtain the updated sequence information. We found that a few published amino acid sequences differ at one or more positions from their GenBank/EMBL entry. Again, we have communicated with the primary author to confirm the correct sequences.

The multiple alignment of the amino acid sequences was obtained by a series of pairwise alignments combined and adjusted by eye into larger and larger subsets of similar sequences. The process of combining and adjusting by eye was aided by modified versions of the MOTIF program (67) and the ALIGN program (68). The GAP and BESTFIT programs, from UWGCG (University of Wisconsin Genetic Computer Group) (69), initially generated the pairwise alignments, adjusted for maximum alignment that allowed for a considerable number of gaps. We then compressed these alignments by eye to give a more contiguous alignment. The alignment of the sequences for optimal similarity is straightforward in the areas of relatively conserved structure, but is much more arbitrary in the more varied sequence areas. The alignment of the varied areas should therefore be regarded as less than optimal in view of the difficulties concerned with multiple alignments in these areas.

Finally, we invite further correction from readers, and welcome suggested revisions and alternative alignments.

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Classification of DNA polymerases

			References
A.	**Family A DNA polymerases**		
	1.	**Bacterial DNA polymerases**	
		a) *E. coli* DNA polymerase I	(1)
		b) *Streptococcus pneumoniae* DNA polymerase I	(2)
		c) *Thermus aquaticus* DNA polymerase I	(3)
	2.	**Bacteriophage DNA polymerases**	
		a) T5 DNA polymerase	(4)
		b) T7 DNA polymerase	(5)
		c) Spo2 DNA polymerase	(6)
	3.	**Mitochondrial DNA polymerase**	
		Yeast mitochondrial DNA polymerase (MIP1)	(7)
B.	**Family B DNA polymerases**		
	1.	**Bacterial DNA polymerases**	
		E. coli DNA polymerase II	(8)
	2.	**Bacteriophage DNA polymerases**	
		a) PRD1 DNA polymerase*	(9,10)
		b) ϕ29 DNA polymerase*	(11)
		c) M2 DNA polymerase*	(12)
		d) T4 DNA polymerase	(13)
	3.	**Eukaryotic DNA polymerases**	
		a) Human DNA polymerase alpha	(14)
		b) Yeast DNA polymerase I	(15)
		c) Yeast DNA polymerase II	(16)
		d) Yeast DNA polymerase III (delta)	(17)
		e) Yeast DNA polymerase Rev3	(18)
	4.	**Viral DNA polymerases**	
		a) Herpes-1 DNA polymerase	(19)
		b) Human cytomegalovirus DNA polymerase	(20)
		c) Epstein-Barr virus DNA polymerase	(21)
		d) Varicella-Zoster virus DNA polymerase	(22)
		e) Fowlpox virus DNA polymerase	(23)
		f) Vaccinia virus DNA polymerase	(24)
		g) Autographa californica nuclear polyhedrosis virus (AcMNPV) DNA polymerase	(25)
		h) Adenovirus-2 DNA polymerase*	(26)
		i) Adenovirus-7 DNA polymerase*	(27)
		j) Adenovirus-12 DNA polymerase*	(28)
	5.	**Eukaryotic linear DNA plasmid encoded DNA polymerases**	
		a) S-1 maize mitochondrial DNA polymerase*	(29)
		b) *Kluyveromyces lactis* plasmid pGKL1 DNA polymerase*	(30)
		c) *Kluyveromyces lactis* plasmid pGKL2 DNA polymerase*	(31)
		d) *Claviceps purpurea* plasmid pCLK1 DNA polymerase*	(32)
		e) *Ascobolus immersus* plasmid pAI2 DNA polymerase*	(33)
C.	**Family C DNA polymerases**		
		Bacterial replicative DNA polymerases	
		a) *E. coli* DNA polymerase III α subunit	(34)
		b) *Salmonella typhimurium* DNA polymerase III α subunit	(35)
		c) *Bacillus subtilis* DNA polymerase III	(36)
D.	**Family X DNA polymerases**		
		a) Rat DNA polymerase β	(37)
		b) Human DNA polymerase β	(38,39)
		c) Human terminal deoxynucleotidyltransferase (TdT)	(40)
		d) Bovine terminal deoxynucleotidyltransferase (TdT)	(41)
		e) Mouse terminal deoxynucleotidyltransferase (TdT)	(41)

Table 1. The main families and subclassifications of DNA polymerases. Those DNA polymerases marked with a star (*) are protein-primed DNA polymerases.

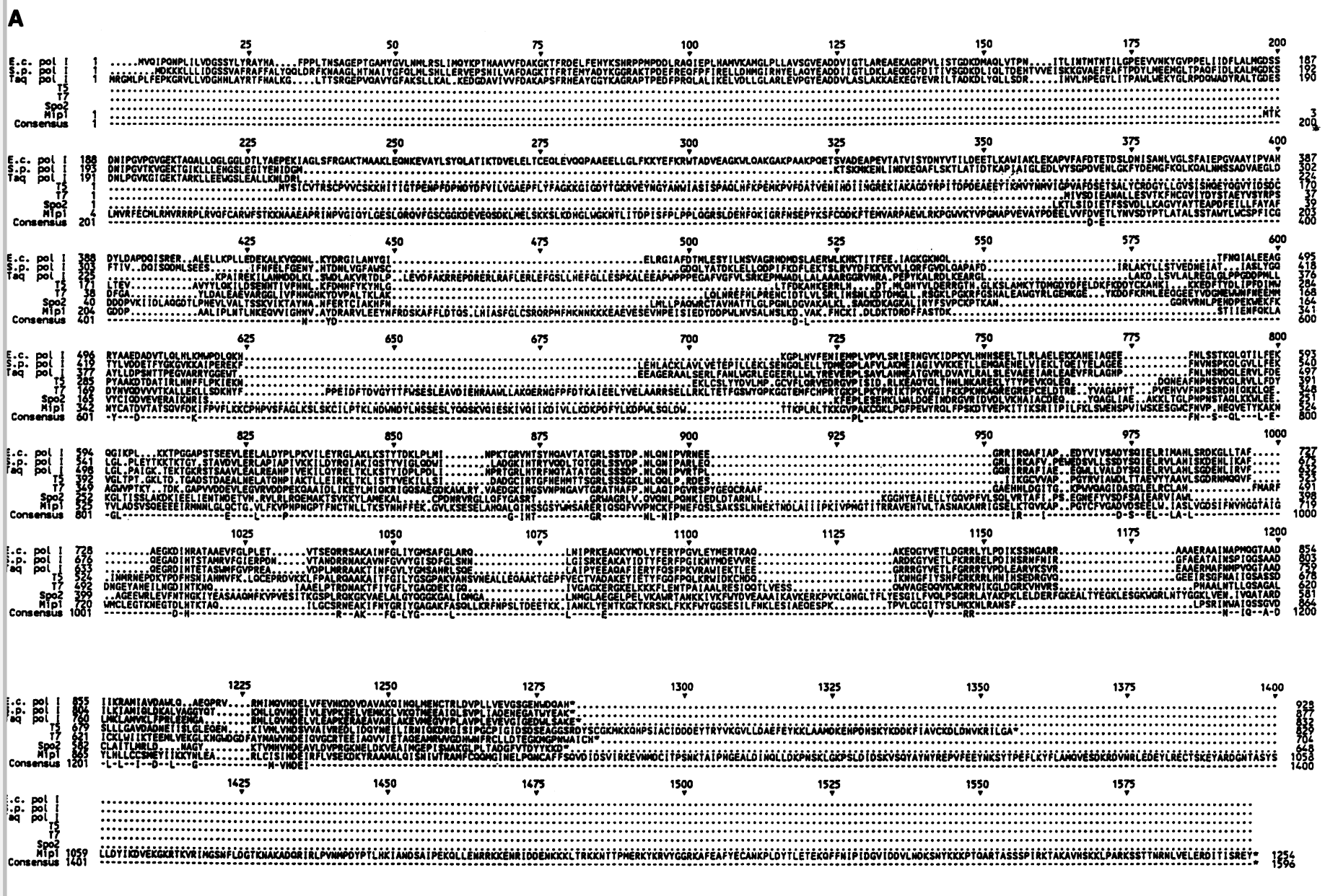

Figure 1A. Family A DNA polymerases—*E. coli* DNA pol. I (E.c. pol I)(1), *Streptococcus pneumoniae* DNA pol. I (S.p. pol I)(2), *Thermus aquaticus* DNA pol. I (Taq pol I)(3), T5 DNA pol. (4), T7 DNA pol. (5), Spo2 DNA pol. (6), and yeast mitochondrial DNA pol. (MIP1)(7).

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