Minireview

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Eukaryotic DNA Polymerases: Proposal for a Revised Nomenclature*

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In 1975, a Greek letter nomenclature system was introduced to designate DNA polymerases from mammalian cells (1). Ten years ago, progress in the biochemical analysis of eukaryotic DNA polymerases and in the isolation of their genes, particularly in the yeast *Saccharomyces cerevisiae*, necessitated a revision of the Greek letter nomenclature system and an expansion to include all eukaryotic organisms (2). Until a few years ago, this system sufficed to designate the six known DNA polymerases α, β, γ, δ, ϵ, and ζ.

Three lines of research have greatly expanded the number of DNA polymerases in the last two years. First, with the advent of the human and mouse genome projects, sequence analysis allowed the identification of additional putative DNA polymerases related to *Escherichia coli* Pol I[1] and mammalian Pol β (3–6). Second, the realization that *E. coli* UmuC and DinB, yeast *RAD30*, and the human xeroderma pigmentosum variant genes encode DNA polymerases has led to the identification of several additional DNA polymerases in this superfamily (7–11). Third, advanced search algorithms based on DNA polymerase structure-function relationships have allowed the prediction of additional putative DNA polymerases, which prediction was later confirmed by biochemical analysis (12–14). This rapid proliferation of DNA polymerases, either predicted from search algorithms or experimentally verified, resulted in an inevitable confusion and contradiction in the naming of these enzymes. Therefore, the scientists active in this field are proposing a revised nomenclature to resolve contradictions in polymerase designations and to ensure that the naming of subsequent enzymes be under the advice of an established nomenclature committee.

Resolution of Contradictions in Current Literature

A novel human DNA polymerase in the X family of DNA polymerases had independently been identified by several groups, but the enzyme was named Pol β2 by one group (15) and Pol λ by two other groups (4, 6). In conformity with the new proposed rules for naming DNA polymerases, the name Pol λ will be adopted for this enzyme. A putative DNA polymerase with homology to *E. coli* DNA polymerase I, which had been designated Pol θ for the human enzyme (3) but Pol η for the *Drosophila* enzyme (16, 17), will be called Pol θ as Pol η is already used to designate the unrelated yeast *RAD30* encoded DNA polymerase (10). A human homologue of *E. coli* DinB, *i.e.* the human *DINB1* gene, had independently been identified by several groups. However, the enzyme was designated DNA Pol θ by one group (18) and Pol κ by other groups (19–21). We have chosen to adopt the name Pol κ for the mammalian DINB1 enzyme. Finally, the name Pol κ had also been assigned to a DNA polymerase encoded by the *S. cerevisiae TRF4* gene, required for sister chromatid cohesion (14). To maintain a coherent and logical nomenclature across eukaryotic phyla, the DNA polymerase encoded by *TRF4* has been renamed Pol σ. Table I gives an overview of the currently known eukaryotic DNA polymerases.

Proposal of New Rules

To avoid future confusion and contradictions in DNA polymerase designations, we are proposing the following rules. 1) The human genome nomenclature committee (www.gene.ucl.ac.uk/

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[1] The abbreviation used is: Pol, polymerase.

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TABLE I
Proposed nomenclature for eukaryotic DNA polymerases
S. cerevisiae genes (in italics) and conflicting names are listed under "Other Names." See text for details.

Greek name	HUGO name	Class	Other names	Proposed main function
α (alpha)	POLA	B	*POL1*	DNA replication
β (beta)	POLB	X		Base excision repair
γ (gamma)	POLG	A	*MIP1*	Mitochondrial replication
δ (delta)	POLD1	B	*POL3*	DNA replication
ε (epsilon)	POLE	B	*POL2*	DNA replication
ζ (zeta)	POLZ	B	*REV3*	Bypass synthesis
η (eta)	POLH	Y	*RAD30*, XPV	Bypass synthesis
θ (theta)	POLQ	A	mus308, eta	DNA repair
ι (iota)	POLI	Y	RAD30B	Bypass synthesis
κ (kappa)	POLK	Y	DinB1, theta	Bypass synthesis
λ (lambda)	POLL	X	*POL4*, beta2	Base excision repair
μ (mu)	POLM	X		Non-homologous end joining
σ (sigma)	POLS	X	*TRF4*, kappa	Sister chromatid cohesion
	REV1L	Y	*REV1*	Bypass synthesis
	TDT	X		Antigen receptor diversity

nomenclature; E-mail: nome@galton.ucl.ac.uk) has agreed to coordinate the nomenclature of all eukaryotic DNA polymerases. A polymerase should only be given a Greek letter designation with approval by the HUGO nomenclature committee. Greek letter denominations for putative DNA polymerases can be reserved pending experimental verification. As usual, the burden of proof remains acceptance of the experimental work in a peer-reviewed scientific journal. 2) In general, all DNA polymerases will follow the one gene→one polymerase rule. However, the *TRF* family of DNA polymerases, required for sister chromatid cohesion, will constitute an exception to this rule. Studies in *S. cerevisiae*, *Schizosaccharomyces pombe,* and mammalian cells have shown these to be multigene families with two members (*TRF4* and *TRF5*) in *S. cerevisiae* (14), as many as six possible family members (the *cid* genes) in *S. pombe* (22), and at least two identified family members in human cells. Because of the potential for a multitude of DNA polymerases involved in sister chromatid cohesion and related processes, the *TRF4*-related DNA polymerases will all be designated Pol σ, with each individual family member designated with a suffix, *i.e.* Pol σ1. 3) A class of nucleotidyltransferases with *S. cerevisiae REV1* as founding member uniquely inserts deoxycytidylate residues, preferentially opposite abasic template sites (23). Because of its unique enzymatic character, no polymerase designation has been given to this enzyme even though sequence-based considerations place it in the Y class of DNA polymerases (24). Similar considerations apply to terminal deoxynucleotidyltransferase, an X class template-independent enzyme (Table I).

Classification of DNA Polymerases and Occurrence across Eukaryotic Phyla

DNA polymerases can be classified in six main groups based upon phylogenetic relationships with *E. coli* Pol I (class A), *E. coli* Pol II (class B), *E. coli* Pol III (class C), Euryarchaeotic Pol II (class D), human Pol β (class X), and *E. coli* UmuC/DinB and eukaryotic *RAD30*/xeroderma pigmentosum variant (class Y) (24–27). All known eukaryotic enzymes are either class A, class B, class X, or class Y enzymes (Table I). No eukaryotic homologs of class C or class D DNA polymerases were detected (www.ncbi.nlm.nih.gov/) despite detailed sequence searches using the PSI-BLAST program (28, 29).

For each distinct human DNA polymerase we searched for putative orthologs in the completely sequenced genomes of *S. cerevisiae*, *S. pombe*, *Drosophila melanogaster*, *Caenorhabditis elegans*, and *Arabidopsis thaliana* (Table II). Clear and unambiguous orthologs exist in all eukaryotes for the class B enzymes Pol α, Pol δ, and Pol ε, required for nuclear DNA replication, and also for Pol ζ, a class B enzyme involved in mutagenic DNA replication. These enzymes have been extensively reviewed and will not further be discussed here (30–34).

Pol β, Pol λ, and Pol μ—Two enzymes of this set of related DNA polymerases may be involved in short-patch DNA excision repair. Both human Pol β and human Pol λ show deoxyribose phosphate lyase activity, indicative of their ability to process intermediates in the DNA glycosylase-initiated repair of damaged bases (35, 36). A function for Pol μ in somatic hypermutation has been proposed based upon its low fidelity of DNA synthesis *in vitro* and its cell type-specific expression pattern in mammals (5, 37). Moreover, a more general role of Pol μ in non-homologous end joining of double-stranded DNA breaks has also been proposed (38). Interestingly, neither of these three enzymes is found in *D. melanogaster* or in *C. elegans*, suggesting that base damage in these organisms is exclusively repaired by the long-patch mechanism, requiring the nuclease FEN1 and the replication clamp proliferating cell nuclear antigen (39, 40). The virtual lack of sensitivity to several DNA-damaging agents in a *S. cerevisiae* null mutant of the single β-like DNA polymerase gene *POL4*, which appears to be the ortholog of Pol λ, strongly suggests that base damage is efficiently repaired by the long-patch base excision repair pathway in this organism (41, 42). Contrasting with *S. cerevisiae*, the β-like enzyme in *S. pombe* (SPAC2F7.06c) is the apparent ortholog of Pol μ (Table II). The metazoan but not the yeast Pol λ/μ proteins have consensus BRCT (BRCA1) domains at their N termini.

Pol η, Pol ι, and Pol κ—These three related DNA polymerases are required for bypass of various forms of DNA damage (for recent reviews, see Refs. 43–49). The damage specificity of these enzymes shows limited overlap (10, 18, 19, 21, 50–55). Pol η and Pol ι appeared to have evolved through a lineage-specific duplication in animals, so these two paralogs together should be considered orthologous to the single counterpart in other organisms. Orthologs are found in each of the five eukaryotic organisms investigated (Table II). Surprisingly, Pol ι was also found to possess deoxyribose-phosphate lyase activity, like Pol β and Pol λ, perhaps implicating it in a specialized form of base excision repair (56–58). In contrast to the three bypass enzymes Pol η, Pol ι, and Pol κ, the related deoxycytidylate transferase Rev1, which is required for mutagenesis, is clearly represented in each organism (34) (Table II).

Pol σ—This DNA polymerase, which is very distantly related to the other members of the Pol X superfamily, is represented by two closely related paralogs in human, *S. cerevisiae*, *D. melanogaster,* and *S. cerevisiae,* four paralogs in *S. pombe,* and one highly conserved version in *C. elegans* and *A. thaliana* (Table II). In addition, humans have at least two, *C. elegans* at

TABLE II
Orthologs of human DNA polymerases in five completely sequenced eukaryotic organisms

Polymerases are grouped by class and by proposed function. Probable orthologous relationships were established by detecting bi-directional, genome-specific best hits in BLAST searches (62). For each organism, we list the probable ortholog by gene name or GenBank accession number, followed by the lengthf the protein. For the Y class polymerases, the orthologous relationships were determined by phylogenetic analysis (24, 63).

Class	Human Polymerase - Access. # -a.a.	*D. melanog.* Access. # –a.a.	*C. elegans* Access. # –a.a.	*S. cerevisiae* Gene –a.a.	*S. pombe* Gene –a.a.	*A. thaliana* Access. # –a.a.
B	α - CAA29920 - 1462	AAB24152 –1490	CAB97239 –1443	*POL1* -1468	*Pol1* –1465	BAB10944 –1492
	δ - AAA58439 - 1107	CAA61369 –1092	CAB04077 –1081	*POL3* –1097	*Cdc6* –1086	BAA96899 –1081
	ε - AAC19148 - 2286	BAB17608 –2220	CAB04263 –2144	*POL2* –2222	*Cdc20* –2199	AAC77870 –2154
	ζ - AAB88486 - 3130	AAF59191 –1869	AAK31564 –1154	*REV3* –1504	SPAC688.10 –1480	AAG52299 –1871
X	β - BAA06099 - 335	-	-	-	-	-
	λ - CAB65074 - 575	-	-	*POL4* –582	-	CAC21394 –529
	μ -AAF26284 - 494	-	-	-	SPAC2F7.06c –506	-
	σ [a]- BAA24434.2 – 542	AAF46390 –1059 AAF56369 –407	CAB02138 –848	*TRF4* –584 *TRF5* –625	*Cid14* –616 *Cid12* –336 *Cid1* –405 *Cid11* –478	BAB09549 –533
Y[b]	η - BAA81666 - 713	AAF51794 –885	AAB70988 –603	*RAD30* –632	*Eso1* –872	AAC79146 –689
	ι - AAD50381 - 715	AAF54198 –737				
	κ - AAF02540 - 870	-	AAA65458 –598[c]	-	SPCC553.07c –547[c]	AAF76444 –435
	Rev1 – BAB21441 - 1250	AAF47401 –995	CAA86844 –1027	*REV1* –985	SPBC215.16c –935	AAC79145 –955
A	γ - BAA12223 - 1239	AAC47658 –1145	CAB60771 –1072	*MIP1* –1280	*Mip1* –1018	-
	θ - AAK39635 - 2724	AAF54858 –2059	AAB93325 –1208	-	-	CAB79987 –1548
	Other Pols			-	-	AAG50942 –1067 BAB01162 –1088

[a] There are two Pol σ genes in human cells; the analysis was carried out with the *TRF4–1* (POLS) gene, which encodes a protein with demonstrated DNA polymerase activity (M. F. Christman, unpublished results).

[b] Pol η and Pol ι appear to have evolved through a lineage-specific duplication in animals, so these two paralogs together should be considered orthologous to the single counterpart in other organisms.

[c] Alternative splice sites to produce larger forms of Pol κ from *S. pombe* and *C. elegans* have been proposed (45).

least nine, and *A. thaliana* at least one more distant members of this family of (predicted) polymerases (13).[2] Detailed phylogenetic analysis of this family remains to be performed. Pol σ is required for sister chromatid cohesion. DNA polymerase activity has only been demonstrated in the *S. cerevisiae TRF4* gene product and the human TRF4–1 gene product (14).[3]

Pol θ—This DNA polymerase is unique in that the N-terminal domain contains the seven conserved motifs of the DNA and RNA helicase superfamily II, whereas the C-terminal shows strong sequence similarity to *E. coli* DNA polymerase I. Studies with a *Drosophila* Pol θ mutant, designated mus308, suggest a role for this enzyme in DNA repair of interstrand cross-links (59, 60). Fractionated extracts from *Drosophila* mus308 embryos lack a specific DNA polymerase activity present in extracts from wild type, suggesting that mus308 encodes a DNA polymerase (61). This bipartite DNA polymerase is not found in the two yeasts, but putative orthologs were detected in the other three eukaryotic species (Table II).

Pol γ—Surprisingly, no ortholog for the mitochondrial DNA polymerase could be detected in *A. thaliana*. This could either indicate a gap in the data base for this organism or alternatively that mitochondrial DNA replication in plants is either performed by one of the other known DNA polymerases or by a novel DNA polymerase. Interestingly, the BLAST search for Pol θ in *A. thaliana* returned (in addition to the putative ortholog of Pol θ) two class A DNA polymerases with limited sequence similarity to Pol θ (E value of 10^{-15}) but very strong sequence similarity to bacterial DNA polymerase I (E values of 10^{-43}–10^{-48}). Possibly, these two DNA polymerases could function in DNA replication of mitochondrial and/or chloroplast DNA.

Additional Putative DNA Polymerases

As mentioned above, two putative DNA polymerases exist in *A. thaliana* for which no orthologs have been found in human. One or both of these may well be required for replication of chloroplast DNA. Otherwise, additional enzyme(s) remain to be identified for replication of chloroplast DNA. Finally, the *S. cerevisiae POL5* gene, as well as the homologous *S. pombe Pol5* gene, shows only limited sequence similarity with class B DNA polymerases (30). It contains a sequence that is conserved in the two yeasts and resembles the Mg^{2+} binding motif characteristic of the catalytic center of class B DNA polymerases. However, these proteins show significant sequence similarity to eukaryotic leucine zipper-containing transcription factors such as human MYBB1A. In accordance with the proposed new nomenclature rules this putative DNA polymerase has been provisionally designated Pol ϕ and the name POLF reserved with the HUGO nomenclature committee pending experimental verification.

[2] E. V. Koonin, unpublished observations.

[3] M. F. Christman, unpublished results.

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