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An Insight into the Replication Mechanism of Smallpox and Monkeypox Viruses

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Abstract

Poxviruses are a family of large, enveloped DNA viruses that infect large numbers of vertebrates and invertebrates, causing severe disease. Some prominent members of the family, viz. variola virus (causative agent of smallpox), and monkeypox (mpox) virus (causes human mpox) are of great concern globally. The crucial enzyme, viz. the DNA polymerase (pol) involved in the multiplication of these viruses in human cells, is studied and found that it shows striking similarities to most of the DNA pols already reported from prokaryotes and eukaryotes and their pol domain uses the same catalytic amino acids in their active sites as reported for other DNA pols. For example, the smallpox and mpox viral catalytic amino acids in their pol catalytic core regions are the same, viz. -M**Q**$^{-4}$YTY**K**^{1}IIANSV**Y**^{8}**G**LM- and-M**Q**$^{-4}$YTY**K**^{1}IVANSV**Y**^{8}**G**LM-, respectively and are also the same as that of the host enzymes, viz. the human replicative δ and ε DNA pols, viz. -R**Q**$^{-4}$LAL**K**^{1}VSANSV**Y**^{8}**G**FT- and –L**Q**$^{-4}$LAH**K**^{1}CILNSF**Y**^{8}**G**YV-, respectively. Furthermore, the poxviral proofreading (PR) exonuclease domain is made up of the same active site amino acids as in other DNA/RNA pols, including the host replicative DNA pols, and belongs to DEDD(Y) superfamily of PR exonucleases. In spite of their active site similarities, the smallpox and mpox viral replicative DNA pols showed only 23.75 and 23.69 per cent identities, respectively, to the human replicative δ pol. In contrast, the regulatory zinc-binding motifs (ZBMs) which are typically found in human and other eukaryotic replicative pols (α, δ, ε) at their C-terminal domains (CTDs) are absent in these poxviral DNA pols, but a HNH type homing endonuclease motif, which is identified in the poxviral pols, is absent in humans and other eukaryotic replicative pols. Presently approved vaccines and antivirals for smallpox and mpox are also discussed.

Keywords: Smallpox; Monkeypox; Variola virus; Vaccinia virus; Mpox virus; DNA polymerase; Polymerase active site; Proofreading exonuclease active site; Cidofovir; Brincidofovir; Ribavirin

1. Introduction

Depending on the nature of their genetic material, viruses are broadly classified into RNA or DNA viruses. In spite of the major difference in their genetic material, both equally cause serious human diseases, including pandemic ones. For example, some of the pandemic ones, like human immunodeficiency viruses (HIVs), human influenza viruses, human respiratory syncytial viruses, SARS-CoVs, etc., are caused by RNA viruses whereas some of the other serious human diseases, like Hepatitis B (Herpadnaviruses), Herpes simplex virus, Chickenpox (Herpesvirus), Smallpox and Monkeypox (Poxviruses), Respiratory diseases (Adenoviruses), Cervical cancer (Papillomaviruses), etc., are caused by DNA viruses. Based on the structure of their genome and replication strategies, the RNA and DNA viruses are further classified into three main groups: i) double-stranded (ds) RNA (dsRNA) viruses, ii) positive-sense single-stranded RNA (+ssRNA) viruses, and iii) negative-sense single-stranded RNA (-ssRNA) viruses and i) ds DNA viruses (e.g., Poxviruses, Herpesviruses), ii) ss DNA viruses (e.g., Parvoviruses, Adeno-associated viruses), and iii) circular-dsDNA viruses, (Pararetroviruses, e.g., Cauliflower mosaic virus of plants, Hepadnaviruses of vertebrates). As both RNA and DNA viruses cause serious human diseases, it is imperative to understand the fundamental aspects of their lifecycles and replication mechanisms to develop cost-effective vaccines and antiviral drugs to contain the spread of these viruses.

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Among the DNA viruses, the poxviruses are the largest of all known animal viruses (sizes ranging from 220–450 nm long, 140–260 nm wide and 140–260 nm thick) and are also the deadliest ones. They infect most of the vertebrates and invertebrates, causing a variety of diseases of veterinary and medical importance [1]. They are enveloped viruses and possess ds DNA genomes and are mostly oval or brick-shaped. Their genomes comprise of a single, linear molecule of ds DNA of 128–375 kbp with ~200 distinct genes. It is interesting to note that their ds DNA genomes do not have free ends, but are covalently-closed with hairpin-like structures at their ends. These hairpin termini are AT-rich, incompletely base-paired and exist in inverted and complementary forms.

The poxviruses belong to the family of Poxviridae. The poxviridae family is further classified into two subfamilies, viz. Chordopoxvirinae, which infect vertebrates, and Entomopoxvirinae, which infect insects. The subfamilies are further classified into different genera. For example, there are 18 recognized genera in the Chordopoxvirinae subfamily and 4 in the Entomopoxvirinae subfamily (Table 1). Chordopoxviruses have a restricted and specific host array and only 4 of them are known to infect humans also. It should be noted that the poxviruses are resistant to ambient temperatures and may survive many years in dried scabs. Some of the poxviruses have a limited host range, but others are capable of infecting a wide range of related animals as well. Therefore, these viruses are generally placed into specific groups, largely based on the type of animal(s) they infect. It is interesting to note that humans are the sole hosts for two of the poxviruses, viz. variola (smallpox) and molluscum contagiosum.

Table 1 Classification of Poxviruses

Family: Poxviridae

Subfamily 1: Chordopoxvirinae **(from the Phylum *Chordata;* Vertebrate hosts)**

1. *Genus: Avipoxvirus* ***(Bird)#***
2. *Genus: Capripoxvirus* ***(Goat)***
3. *Genus: Centapoxvirus* ***(From central Africa, e.g.,*** **yokapox virus)**
4. *Genus: Cervidpoxvirus* ***(Deer)***
5. *Genus: Crocodylidpoxvirus* ***(Crocodile)***
6. *Genus: Leporipoxvirus* ***(Hare)***
7. *Genus: Macropopoxvirus* ***(Large footed)***
8. *Genus:* ***Molluscipoxvirus**** ***(Clam, Snail)***
9. *Genus: Mustelpoxvirus* ***(Weasel)***
10. *Genus: Oryzopoxvirus* ***(Rodents)***
11. *Genus:* ***Orthopoxvirus**** ***(Gk = straight)***
12. *Genus:* ***Parapoxvirus**** ***(Gk = beside or next to)***
13. *Genus: Pteropopoxvirus* ***(wing footed)***
14. *Genus: Salmonpoxvirus* ***(Salmon)***
15. *Genus: Sciuripoxvirus* ***(Squirrel)***
16. *Genus: Suipoxvirus* ***(Swine)***
17. *Genus: Vespertilionpoxvirus* ***(Bat)***
18. *Genus:* ***Yatapoxvirus**** ***(Yaba monkey)***

Subfamily 2: Entomopoxvirinae **(**Gk. *Entomon = Insect*, **Insect hosts)**

1. *Genus: Alphaentomopoxvirus*
2. *Genus: Betaentomopoxvirus*
3. *Genus: Deltaentomopoxvirus*
4. *Genus: Gammaentomopoxvirus*

Adapted from McInnes *et al.* [2]

#The genus Avipoxvirus, under natural conditions, infects and causes diseases in avians only; e. g., fowlpox, pigeonpox, and turkeypox viruses are closely related and are not strictly host-specific.

*Those which infect humans are found only among four genera of the Chordopoxvirinae subfamily, viz. Orthopoxvirus, Parapoxvirus, Molluscipoxvirus and Yatapoxvirus (highlighted in red).

Molluscum contagiosum virus is the only member of the genus Molluscipoxvirus and humans are the natural reservoirs for the virus. The human infections are restricted to the skin and affect primarily children and immuno-compromised adults. The unique feature of the virus is; it is restricted to human keratinocytes which build the outer layer of the skin.

Members of the genus, Yatapoxvirus (Yata is derived from the two recognized members of the class, viz. the ***ya***ba monkey tumour virus and ***ta***napox virus, which infect primates in equatorial Africa. Infections can spread to humans by insect vectors

The yaba monkey tumor virus and yaba-like disease virus, like all members of the genus Yatapoxvirus, are considered as potential human pathogens.

The orthopox- and parapoxviruses of the Chordopoxvirinae subfamily are further classified into Zoonotic and Non-zoonotic types, as shown in Table 2.

Table 2 Classification of Orthopox- and Parapoxviruses

Genus: Orthopoxvirus	
Zoonotic types	**Non-zoonotic types**
1. Monkeypox virus	1. Variola virus
2. Vaccinia virus	2. Volepox virus
3. Buffalopox virus	3. Ectromelia virus
4. Camelpox virus	4. Raccoonpox virus
5. Cowpox virus	5. Skunkpox virus
6. Elephantpox virus	6. Uasin Gishu disease virus
	7. Taterapox virus
Genus: Parapoxvirus	
Zoonotic types	**Non-zoonotic types**
1. Bovine papular stomatitis virus	1. Auzduk disease virus
2. Orf virus (Sheep)	2. Parapoxvirus of red deer
3. Pseudocowpox virus (milker's nodules)	3. Chamois contagious ecthyma virus
4. Sealpox virus	

1.1. Smallpox Virus (Variola Virus)

Among the poxviral diseases, the smallpox is the most severe one and also highly contagious. It easily spreads from person to person by contact. It is caused by the smallpox virus which is generally known as variola virus (VARV, variola is the Latin name for smallpox). It is a member of the Poxviridae family and Chordopoxvirinae subfamily and belongs to the genus Orthopoxvirus. [The term "smallpox" is used to distinguish it from the "greatpox" (syphilis)]. It is interesting to note that the smallpox disease has been one of the deadliest diseases in human history and it killed about millions of people in the 20th century alone. However, in the 1980s, after an intensive immunization program with a vaccine prepared from the vaccinia virus (VACV), the World Health Organization (WHO) declared the disease eradicated. On 26 October 1979, WHO announced the eradication of smallpox, and it was officially declared on 8 May 1980, during its 33rd assembly. (VACV is closely related to VARV, but relatively nonpathogenic and therefore, used in the preparation of smallpox virus vaccines. It is also widely used as a model for poxviruses in the laboratory to understand the biochemistry and molecular biology of the VARV, in general). As the routine vaccination for smallpox ended worldwide in the 1970s, most of today's population lacks immunity against the virus and hence, the smallpox attack could be especially harmful and deadly. It is also suggested that the ending of the vaccination programme for smallpox, accidentally created an opening for the emerging human mpox attacks in recent times. And thus, in the absence of the smallpox vaccine, the mpox virus has certainly proven its ability to evolve freely and spread widely, leading to today's international emergency situation [3].

Poxviruses have developed a distinct replication strategy in human cells, i.e., unlike other DNA viruses, they replicate in the cytoplasm itself. The genomes of ~30 poxviruses have been completely sequenced, including several strains of variola and vaccinia viruses. At least two major variants of the VARVs are reported, and they cause two different forms of the smallpox disease, viz. i) Variola major: it is a more severe one with case-fatality rates of 30%–40%, and ii) Variola minor: it is less severe with a much-reduced case-fatality rates of 1% or less. Outbreaks of the Variola major were the only known type until the end of the 19th century. Most of those who survived the Variola major had distinctive residual facial pockmarks, and some were blind. However, at the genome level, the two variants are very similar. For example, they differ only in about <2% of the roughly 1,85,000 unique DNA nucleotides and almost all of the encoded proteins are essentially identical in both [4].

1.2. Mpox Virus

1.2.1. Infection and Diagnosis

Mpox virus disease has now become an emerging poxviral disease and is spread worldwide by the mpox virus. It was first discovered in Denmark (1958) in monkeys kept for research. However, the first reported human case of mpox virus disease was a nine-month-old boy in the Democratic Republic of the Congo (DRC) in 1970. Initially, the mpox virus was found mainly in the tropical rainforests in Central, East and West Africa, where small mammals such as squirrels, Gambian pouched rats, dormice, and various species of monkeys acted as carriers of the mpox virus.

The mpox virus is also a brick- or oval-shaped virus like the smallpox virus, ranging in size from 200-250 nm in diameter. It belongs to the Poxviridae family along with the other poxviruses, like variola, vaccinia, camelpox and cowpox viruses; all of which are pathogenic to humans [5]. A recent WHO report shows that the human mpox cases are escalating worldwide and have emerged as a significant threat to the global population. In 2022, human mpox virus has spread worldwide, causing 99,581 mpox cases in 121 countries [6]. Therefore, in August 2024, the WHO declared it as a *'public health emergency of international concern'* for the first time in May 2022 and the second time in August 2024. Therefore, for this epidemic to be controlled, the epidemiology, its lifecycle, multiplication mechanism in human cells and genetics must be better understood. Interestingly, as its genome and lifecycle are very closely related to vaccinia and variola viruses, their vaccines and antiviral drugs maybe of some use to control the spread of the virus. Furthermore, as the mpox virus is a close relative of the smallpox virus and also due to its antigenic similarity to the smallpox virus, smallpox vaccines cross-protect against mpox viral infections too.

Even though originally it was a zoonotic virus, now it has been found that it is capable of human-to-human transmission too and spreads through close contact. Transmission occurs through exposure to bodily fluids, lesions on the skin or on internal mucosal surfaces such as in the mouth or throat, respiratory particles and contaminated objects. Its clinical presentation is similar to smallpox, i.e., like 10-14 days of incubation followed by formation of skin rashes. The rashes are painful with enlarged lymph nodes with headache, muscle ache, back pain, sore throat and fever that can progress to severe complications, including pneumonia and encephalitis. Hence, the differentiation of these diseases by clinical presentation alone is quite challenging.

Identification of mpox virus infections in humans is becoming more difficult because of other viral and bacterial infections, with similar conditions. Therefore, it is important to distinguish mpox virus infections from other viral infections, like chickenpox, measles, scabies, herpes, syphilis and other sexually transmitted infections, bacterial skin infections for specific mpox treatments. Testing of blood for mpox virus is not recommended as the viremic phase may have already passed at the time of the onset of rash. Furthermore, antibody detection methods may not be useful as they do not distinguish between different Orthopoxviruses. Therefore, the preferred laboratory test for mpox virus is the detection of the mpox viral DNA by polymerase chain reaction (PCR) techniques like the real-time PCR (RT-PCR). Now, the RT-PCR has become the gold standard for diagnosing the human mpox virus. The U.S. Food and Drug Administration (FDA) has granted Emergency Use Authorization (EUA) to seven diagnostic tests based on RT-PCR [7 and references therein].

1.2.2. Classification of Mpox Virus

The mpox viral strains are classified into two main clades: the more pathogenic Congo Basin (Central Africa) clade (also known as Clade I) and the West African clade (also known as Clade II). Clade I infections are known to be associated with greater disease severity and more pronounced as compared to clade II infections. Furthermore, a recent data has shown that the clade I is capable of increased human-to-human transmission compared to clade II. The Clades I and II are further classified into 2 subclades as Ia and Ib and IIa and IIb. www.who.int/news/item/12-08-2022-monkeypox--experts-give-virus-variants-new-names. The Ib and IIb are evolved variants of I and II, respectively, with the potential for human-to-human transmission. Thus, there are 4 known circulating variants of the virus, as clades Ia, Ib, IIa and IIb [8].

The Clade Ia strain of the virus was the first one to be discovered to infect humans in 1970 from Central Africa. It infected mostly children, and was known to be mainly transmitted animal to human (a zoonotic type).

The Clade Ib strain of the virus was also discovered in Central Africa and is distinguished by its capability of human-to-human transmissions, including through sexual contact. Therefore, this led to a surge of human mpox cases in the late 2023. However, as of August 2024, clade Ib has also been detected beyond Africa. For example, now the Clade Ib has been detected in the United Kingdom, Sweden, Thailand, India, Germany and six other African countries that had never reported mpox infections before. Among the nations, the DRC has been hit particularly hard by the clade Ib. In fact, the country has reported nearly 36,000 suspected infections and more than 1,000 deaths from mpox in 2024.

The Clade IIa strain of the virus is the least-studied one. It has been mainly reported in Guinea, Liberia and Côte d'Ivoire. Its modes of transmissions are not fully understood, but it is likely that it spreads through close contact, and there is no documented evidence of sexual transmission.

The Clade IIb strain of the virus is known to spread from human-to-human, including through sexual contact. It is responsible for the 2022-2023 global outbreaks that has infected more than 90,000 people and continues to infect more people till this day [8].

1.3. Genomes of Smallpox and Mpox Viruses: Salient Features

All poxviruses possess very similar genomic structures, i.e., they all have a linear, ds DNA genome that varies from 130 to 230 kbp. Their genomic DNA contains an identical, but oppositely oriented sequences called inverted terminal repeats (ITRs) at their ends [9, 10]. The ITRs include a set of short tandem repeats and terminal hairpins [11]. The terminal hairpin-like structures connect the linear ds DNA strands into closed termini [12, 13]. It is suggested that these closed termini could protect the genomes from host nucleases and ensure genome's integrity. The terminal hairpin-like structures contain predominantly AT residues and is incompletely based-paired. A central region of the genome is highly conserved among different Orthopoxviruses and the late genes are clustered near the central region. The ends of the genome are hypervariable and may contain extensive deletions and symmetrical sequence rearrangements [14]. It is interesting to note that much of the poxvirus genome encodes gene products that serve to evade the host immune responses.

Different strains of the smallpox viral genomes are completely sequenced. The smallpox viral variant that causes smallpox, Variola major (with an overall fatality rate of ~30%), has a genome that consists of a single, linear, ds DNA molecule that is 1,86,102 bp long with a coding capacity for ~187 proteins (~150 of which are very similar (with >90% identity) between smallpox and vaccinia viruses). It possesses relatively small (725 bp) ITRs containing three 69-bp direct repeat elements. It has a 105-base telomeric end-loop that is maximally base-paired with 17 mismatches [15]. The other smallpox viral variant, viz. Variola minor, causes mild smallpox (with an overall fatality rate of ~1% or less) and its genome varies slightly from the Variola major. It contains a linear ds DNA genome of 1,86,986 bp with ~206 potential ORFs. The smallpox virus genome is contained within a biconcave core, with two lateral bodies on either side [16].

The most studied among the poxviral genomes is the vaccinia viral genome. It is similar to the smallpox virus genome and consists of 1,91,636 bp with a base composition of 66.6% A + T with 198 "major" protein-coding regions and 65 overlapping "minor" regions, for a total of 263 potential genes. Interestingly, it is used in the preparation of smallpox vaccines as it is similar to smallpox, but is less harmful [17]. As in other poxviral genomes, in the vaccinia viral genome also, the two strands of viral DNA molecule are cross-linked at both termini with hairpin-loops and the hairpin termini are AT-rich and exist in inverted-complementary forms and incompletely base-paired. In the case of vaccinia virus, the hairpins are 104 nucleotides in length and contain a 4-nucleotide loop. The hairpin is at the end of long-ITRs containing sets of short, tandemly repeated sequences [18]. Unlike variola virus, in the vaccinia viral genome the long-inverted terminal repeats (LTR) are of about 10 kbp and are found at the distal ends of the genome. The LTRs are further characterized by the presence of direct tandem repeats of a 70-bp sequences, arranged in two blocks of 13 and 17 copies, respectively.

The mpox viral genomic structure also closely resembles that of other Orthopoxviruses. The mpox virus possesses a 1,97,201 bp ds DNA with a G+C content of 33.01%. The virus contains about 190 nonoverlapping open reading frames (ORFs), four of which are located in the ITR sequence. Both terminal regions are variable which include a 6379 bp ITRs with approximately 80 bp long hairpin loop, 70 or 54 bp short, tandem repeats and unique ITR sequences and the coding region [19 and references therein, [20]. Its genome is characterized by a highly conserved central core region, with variable regions at the left and right ends, and tandemly repeated ITRs on both the ends. The central core region of mpox virus shares more than 90% sequence homology with other Orthopoxviruses. The central conserved region encodes "housekeeping" genes involved in transcription, replication and virion assembly. The genes in the terminal regions encode proteins involved in host range and pathogenesis [21]. It is interesting to note that the mpox and smallpox viral genomes are genetically highly similar with a 96.3% identity between them [22].

1.4. Lifecycle of Poxviruses

Poxviruses, like the variola virus that causes smallpox, are transmitted primarily through direct contact with infected persons or through respiratory droplets from an infected person's coughs and sneezes. There are at least five major structural elements that make up the infectious virion: i) Central core, ii) Core wall, iii) Lateral bodies (function(s) not known), iv) Inner membrane, and v) Outer membrane envelope carrying the surface proteins. The central core essentially consists of the viral genome and the viral enzymes essential for early genes transcription.

The lifecycle of poxvirus is unique from other DNA viruses in that they do not enter the nucleus of the infected cells and the whole lifecycle is completed within the host cell cytoplasm itself. After infection, they have an incubation period of 7–17 days. During that time, a massive viral replication takes place in lymphatic tissues resulting in the swelling of lymph nodes. Then it returns to body surfaces (to mucosa and skin with multiple lesions) paving the way for subsequent infections. The lifecycle essentially involves 7 stages: i) Attachment, entry and early genes transcription, ii) Uncoating,

iii) Late genes transcription and replication, iv) Viral assembly, vi) Envelopment of the viral particles by intracellular membranes and maturation of viral particles, and vii) Release of mature virions.

In the first step, the virus binds to its specific receptor on the host cells, viz. the glycosaminoglycans present on the host cell surface act as the receptor for poxvirus attachment (Glycosaminoglycans are anionic polysaccharides and consist of repeating disaccharide units of uronic acid and hexosamine. They include hyaluronan, chondroitin sulphate, dermatan sulphate, heparan sulphate, heparin and keratan sulphate). Senkevich *et al.* [23] found that the entry of the virus was through the membrane fusion and is highly conserved among the poxvirus family, implying that this primary mechanism, developed in their early evolution, remains unchanged.

Expression of the early genes starts in the next step. Viral genes are expressed in two phases: early and late. The early genes encode non-structural proteins, while the late genes encode structural proteins needed for the final assembly of the progeny virions. As mentioned earlier, the viral core contains not only the viral genome, but also the full transcriptional machinery needed to initiate early gene expression *in situ*, including enzymes such as the viral DNA-dependent RNA polymerase (DdRp), capping enzyme, poly(A) polymerase, topoisomerase, and transcription factors. This is evident from the fact that the synthesis of the viral early gene mRNAs starts within minutes after viral entry. The early gene transcripts are extruded through the pores of the viral core and are translated in the host cell cytoplasm. The early genes are ~100 in number which constitute nearly half of the viral genome, encode the proteins needed for uncoating, transcription factors (needed for the subsequent late gene expression), and the full repertoire of enzymes and proteins needed for the replication of the viral genome. After early gene expression, the viral core undergoes a complex process of uncoating in which the wall of the viral core dissolves and the genome is released. Transcription of late genes and DNA replication occurs following release of the genome from the core.

In the final step of the lifecycle, the viral particles are assembled and get enveloped by the intracellular membrane and released. The viral genome, together with viral enzymes and factors required for transcription of the early subset of genes, is packaged in the core of infectious virus particles. Interestingly, the DNA replication proteins, in contrast to those involved in early gene transcription, are not packaged in the virions, but are transcribed and translated from viral mRNAs later. In the early stages of the viral assembly, two distinct infectious viral particles are present: intracellular mature virions (IMVs) and extracellular enveloped virions (EEVs). The IMVs possess a single membrane structure whereas the EEVs possess a double-membrane structure. In addition to the above, these two different viral particles vary in the composition of their envelope membranes and surface glycoproteins. The IMVs are the most abundant viral particles due to the absence of an additional lipid membrane, which gives them a simpler and more robust structure. They are released upon cell lysis and enter new host cells through direct fusion and endocytosis which may be important for their animal-to-animal transmission mode while EEVs move to the peripheral region and are released via membrane fusion [24-26]. It is interesting to note that the EEVs are antigenically distinct from IMVs. Therefore, targeting any stage of the virus lifecycle holds promise for the development of effective antiviral interventions against poxviruses.

1.5. Poxviral Replication Machinery

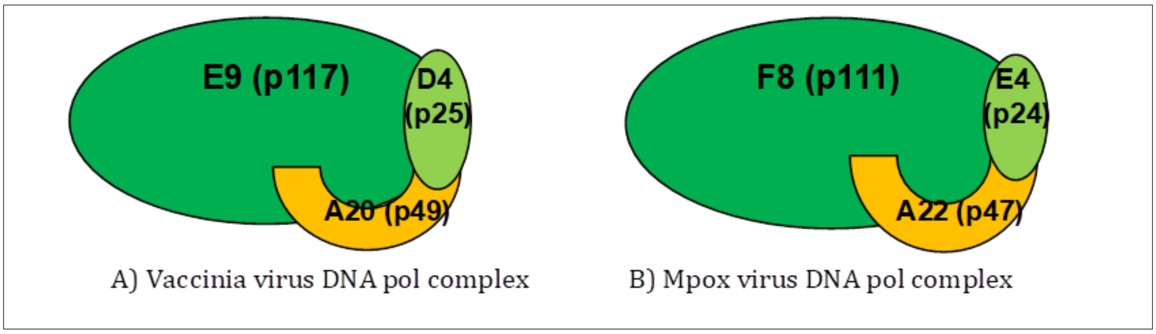
1.5.1. Vaccinia virus Replication Machinery

Genomic DNA replication is the crucial step in the lifecycle of poxviruses. As the vaccinia virus is safer, it is used as a model system to study the biochemistry, genetics and molecular biology of poxviruses, in general. Therefore, a great deal of information is available on its replication machinery. As mentioned elsewhere, unlike other DNA viruses, poxviruses replicate in the cytoplasm and their genomic DNAs encode all the enzymes and proteins that are necessary for their DNA replication. The replication starts with an initiation site on the genomic DNA. Specific replication initiation site is proposed to be possibly within the conserved sequence between the hairpin loop and the direct repeats. Furthermore, it is also proposed that the poxvirus replication is by a primer-dependent mechanism and that too by self-priming. In the self-priming model, a nick in one strand of the poxvirus genome creates a 3′-OH end, which is used as the growing end for the addition of dNTPs that are complementary to the template DNA and further elongated. The presence of the HNH endonuclease motif identified in the poxviral DNA pol may play a role in the initiation step. The elongated strands then fold back, but the replication complex continues to add dNTPs, resulting in the formation of concatemers where multiple copies of the same DNA genome are linked in series. Thus, the viral genomic DNA is proposed to be replicated by a rolling circle mechanism (i.e., where the replication initiator protein nicks a parental strand to create a primer end with 3'-OH for leading-strand synthesis) as long, unbranched, head-to-tail concatemers. The concatamers are further processed by a viral endonuclease, i.e., by the Holliday junction resolvase to produce unit genomes.

For the replication and processing of the genomic DNA of vaccinia virus, at least six virus-encoded enzymes and proteins are required. These include a helicase–primase (encoded by the viral gene, *D5*), a ss DNA-binding protein (encoded by the viral gene, *I3*), a protein kinase (encoded by the viral gene, *B1*), a 117-kDa DNA polymerase (encoded by the viral gene, *E9*), a processivity factor (encoded by the viral gene, *A20*) and an uracil DNA glycosylase (encoded by the viral gene, *E4*). The A20 processivity factor is a non-enzymatic bridging protein that bridges E9 (DNA pol) and D4 protein uracil DNA glycosylase (UDG). (UDG is ubiquitous in biological systems and it functions as DNA repair enzyme by initiating the base-excision-repair pathway, BER). The integration of a UDG in the DNA pol holoenzyme is a unique feature of the poxvirus replication machinery, which might functionally couple the processes of DNA repair to DNA synthesis (Fig. 1A). The B1 kinase phosphorylates a cellular DNA-binding protein called BAF (Barrier to Autointegration Factor) and prevents the latter from blocking the vaccinia viral replication. In addition to the above enzymes, a viral flip endonuclease (FEN1) (encoded by the viral gene, *G5*) participates in ds DNA break repair, a Holliday junction resolvase (encoded by the viral gene, *A22*) resolves the concatemers and a DNA ligase (encoded by the viral gene, *A50*) joins the DNA ends to make an exact copy of the viral genome to be packaged into the viral particles.

1.5.2. Mpox virus Replication Machinery

Similar to the VACV, the mpox virus also replicates its genome in the cytoplasm. The mpox virus possesses a 1.97,201 bp ds DNA genome and encodes ~181 proteins, including all the enzymes and proteins that are required for its DNA replication. Interestingly, the DNA replication machinery is extremely conserved in Orthopoxviruses, and the sequence identity is more than 97% between VACV and mpox virus. Thus, the mpox virus replication machinery is structurally and functionally very similar to VACV. For example, the protein F8 is the DNA pol (E9 in vaccinia virus), A22 is the processivity factor (A20 in vaccinia virus) and E4 is the UDG (D4 in vaccinia virus). These three form the DNA replication machinery, where the U-shaped A22 subunit links F8 to E4 as discussed in vaccinia virus (Fig. 1A). In A22, the two terminal domains, the NTD and CTD, bring close the F8 and E4. A recent cryo-EM studies of the replication machinery of the mpox virus have revealed that in the replication complex, these three proteins, F8-A22-E4 form a novel circular structure [27]. The biochemical assays show that the replication complex with these three proteins is much more efficient in synthesizing DNA than F8 alone, which is consistent with the studies of the homologous VACV DNA pol complex in which the E9-A20-D4 heterotrimer complex synthesizes DNA more efficiently than E9 alone (Fig. 1B).



Figures 1A & 1B Schematic diagrammes showing similarity in the organization of the subunits of vaccinia and mpox virus DNA replication complexes

In vaccinia virus, the catalytic subunit of the DNA pol E9 binds to the essential processivity factor, A20 which is evident from the copurification of it along with DNA Pol E9 subunit. The E9-A20 heterodimer in turn binds to D4 to form the functional polymerase holoenzyme. (The numbers in brackets indicate approximate molecular masses of the subunits).

Similarly, in the mpox virus, the F8 is the catalytic subunit of the DNA pol; A22 is the processivity factor and E4 is the UDG. A22 links E4 to F8 to form the active heterotrimer. (The numbers in brackets indicate approximate molecular masses of the subunits). (During BER, the UDGs in both the pol complexes remove the uracil from DNA, which could arise through misincorporation of dUTP or spontaneous deamination of cytosine. Thus, the UDG initiates the BER pathway by hydrolyzing the glycosidic bond, linking uracil to a deoxyribose sugar, creating an apurinic (AP) site which is cleaved by an AP endonuclease in the subsequent step and repaired.

The main catalytic subunit of the DNA pol complex of vaccinia, variola and mpox viruses invariably follow the same domain organization as shown in Figure 2.

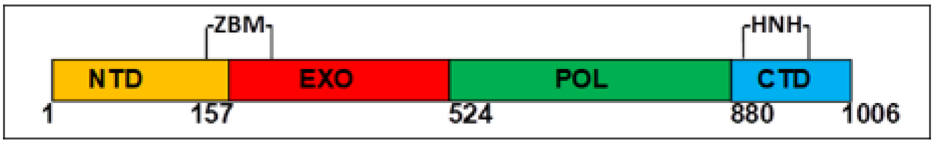


Figure 2 A schematic diagramme showing domain organization of the mpox viral DNA pol

1.6. Vaccines and Antiviral Drugs for the Treatment of Smallpox and Mpox Viruses

Both vaccines and antiviral drugs are available to treat the smallpox and mpox viral diseases. VACV vaccine protects people from smallpox by helping their bodies to develop immunity to smallpox. The smallpox vaccine is not actually made from the smallpox virus, but from VACV, which is also a poxvirus very similar to the smallpox virus, but less harmful. Interestingly, the smallpox vaccine contains live VACV produced from animals, i.e., it is not a killed or weakened like many other viral vaccines. (Other live viral vaccines currently in use are for measles, mumps, rubella, and chickenpox). The *second-generation vaccines* consist of again live VACV, but grown in the chorioallantoic membrane or cell culture techniques. By this way, it is produced in a sterile environment unlike the *first-generation vaccines* that contain the skin bacteria from the animal from where the VACV was grown on. The *third-generation vaccines* are based on attenuated VACV that are much less virulent and carry lesser side effects. The attenuated VACV maybe of a replicating or non-replicating type.

The Modified Vaccinia Ankara (MVA) virus, used in Bavarian Nordic's vaccine (MVA-BN), does not replicate in the body and hence, is much safer and the preferred vaccine for the current mpox outbreak. It is a replication-incompetent variant of the VACV that was developed in Germany through serial passage. The MVA-BN is manufactured by Bavarian Nordic (BN) by growing the MVA in cell culture. The MVA is now the only vaccine that the FDA has explicitly approved for human mpox treatment. Another vaccine recommended by the WHO is LC16m8. It is an attenuated, minimally replicating smallpox vaccine that is derived from the Lister strain of VACV. The WHO has granted 'Emergency use listing (EUL)' for the LC16m for mpox treatments, making it the second mpox vaccine to be recommended by WHO with EUL for the LC16m8 mpox vaccine.

Even though the use of MVA and other vaccines reduced the disease at-risk populations, but failed to deliver complete protection. Therefore, mRNA vaccines have been developed now. The mRNA-1769 vaccine is found to enhance viral control and disease attenuation compared to the MVA vaccine, highlighting the potential for mRNA vaccines to mitigate future pandemic poxviral threats [6]. It was found that among the emerging vaccine platforms, mRNA vaccines offer unprecedented flexibility, speed, and immunogenicity.

The poxvirus vaccines have their own drawbacks. Firstly, the poxvirus vaccines protect mpox, only to a limited extent. Secondly, the vaccine is very expensive (costs ~ $100 per dose). There are not so many countries in Africa and in other third-world countries that can afford this vaccine at this cost. Furthermore, in addition to the cost, the smallpox vaccine was found to be far from ideal. For example, the smallpox vaccine maybe fatal to people with weakened immune systems, as it contains the live VACV and hence, is not suitable for those with weakened immune systems. Therefore, there is an urgent need for the development of cost-effective antiviral drugs for human mpox virus. So far, only a few antiviral compounds have been approved by regulatory authorities. Therefore, it is suggested that the initial efforts to identify inhibitors that should focus on enzymes which play an essential role in the poxvirus replication. Thus, it is important to analyze the active/binding sites of the crucial enzyme(s)/protein(s) in the lifecycle of the virus. And one of them is obviously the viral DNA pol. Therefore, understanding its replication and subsequent resistance mechanisms is fundamental for the development of novel and cost-effective antiviral drugs. Some of the antiviral drugs that are in use currently are discussed in the following section.

Current antiviral treatment options for mpox viral infection are limited to the use of a small number of antiviral drugs that are licensed for the human smallpox disease and is recommended by the CDC, 2024 (www.cdc.gov/poxvirus/mpox/clinicians/treatment.html). These include tecovirimat (commercially known as Tpoxx®) and brincidofovir (BCV, commercially known as Tembexa®), or its active compound cidofovir (CDV, (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine, commercially known as Vistide®). Tecovirimat is the first antiviral agent that was specifically indicated for the treatment of smallpox in adults and paediatric patients and was approved by the FDA (USA) in 2018 [29]. It is an inhibitor of the OPXV F13 envelope protein (also known as VP37), important for viral egress [30, 31].

The second line of antiviral drugs are the DNA pol inhibitors. Among the viral DNA pol inhibitors tested in the *in vitro* laboratory assays are CDV and BCV. They were found to be potent, broad-spectrum antiviral compounds that exhibit anti-poxvirus activities including mpox virus clades I, IIa, and IIb. (CDV is a prodrug, which requires two phosphorylation steps by the host cellular enzymes to be converted into its active form. For example, the phosphorylation by the host kinases, first convert the CDV to CDV-monophosphate (CDV-p) and then to CDV-diphosphate (CDV-pp). The CDV-pp is a competitive inhibitor of DNA pols with respect to dCTP, i.e., the CDV-pp acts as a dCTP analogue during the polymerization reactions. Maximum inhibition of enzyme activity occurs when two or more CDV-pp molecules are incorporated successively. If only one molecule of CDV-pp is incorporated, the replication continues, but at a decreased elongation rate. However, due to the presence of a 3′-OH group, the CDV does not act as a chain terminator, in contrast to all the approved anti-HIV nucleoside inhibitors. Secondly, the CDV-pp could also act as a pyrophosphate (pp) analogue that binds to the pp-binding site on the DNA pol and could prevent the cleavage of the pp group from incoming dNTP, and thus, arresting the chain elongation [23, 32, 33].

Using CDV directly is found to be a problem, as it is a divalent anion exhibiting low bioavailability. Furthermore, in patients with impaired renal function or undergoing renal replacement therapy, its metabolites can accumulate in proximal renal tubular cells, leading to kidney damage. Therefore, in order to overcome these limitations on the use of CDV, its lipid conjugate, viz. the BCV (hexadecyloxypropyl-cidofovir) has been developed. The BCV shows improved bioavailability and significant safety profiles [34]. Furthermore, as it is not a substrate for anion transporters present in renal proximal tubules, its use substantially reduces the risk of drug-induced nephrotoxicity. Upon entry into infected cells, the BCV is converted to CDV and interferes with the DNA pol reactions as discussed above. It was approved by the FDA in 2021 for the treatment of smallpox [35]. Apart from BCV, other compounds based on structural modifications of the CDV have also been developed. For instance, NPP-669 is synthesized by linking a long-chain sulphonate to CDV. This modification improves its solubility in water and its affinity for lipid through the alkyl chain modification. This structural modification is found to enhance the metabolic stability and bioavailability while reducing nephrotoxicity as well [36].

Ribavirin, an inhibitor of RNA-dependent RNA polymerase (RdRp) activity, has also been widely used against RNA and DNA viruses. It is a synthetic purine nucleoside derivative of guanosine. It inhibits guanosine triphosphate formation and thus, prevents capping of viral mRNAs and also blocks viral RdRp activity. Thus, it exhibits a broad-spectrum antiviral activity and inhibits both DNA and RNA viruses such as hepatitis C virus, human influenza viruses A and B, parainfluenza, human respiratory syncytial virus, paramyxovirus, HIV, variola (smallpox), mpox viruses, etc.

2. Material and Methods

The protein sequence data of poxviral DNA pols, eukaryotic replicative pols (α, ε and δ) from yeasts, plants and animals and DNA pols of bacteria and bacteriophages were obtained from PUBMED and SWISS-PROT databases. The advanced version of Clustal Omega was used for protein sequence analysis. Along with the conserved motifs identified by the bioinformatics analysis and from the data already available from biochemical, site-directed mutagenesis (SDM), cryogenic-Electron Microscopy (cryo-EM) and X-ray crystallographic analyses on these replicative pols, are used to identify the possible amino acids at the active sites of smallpox and mpox viral replicative pols.

3. Results and Discussion

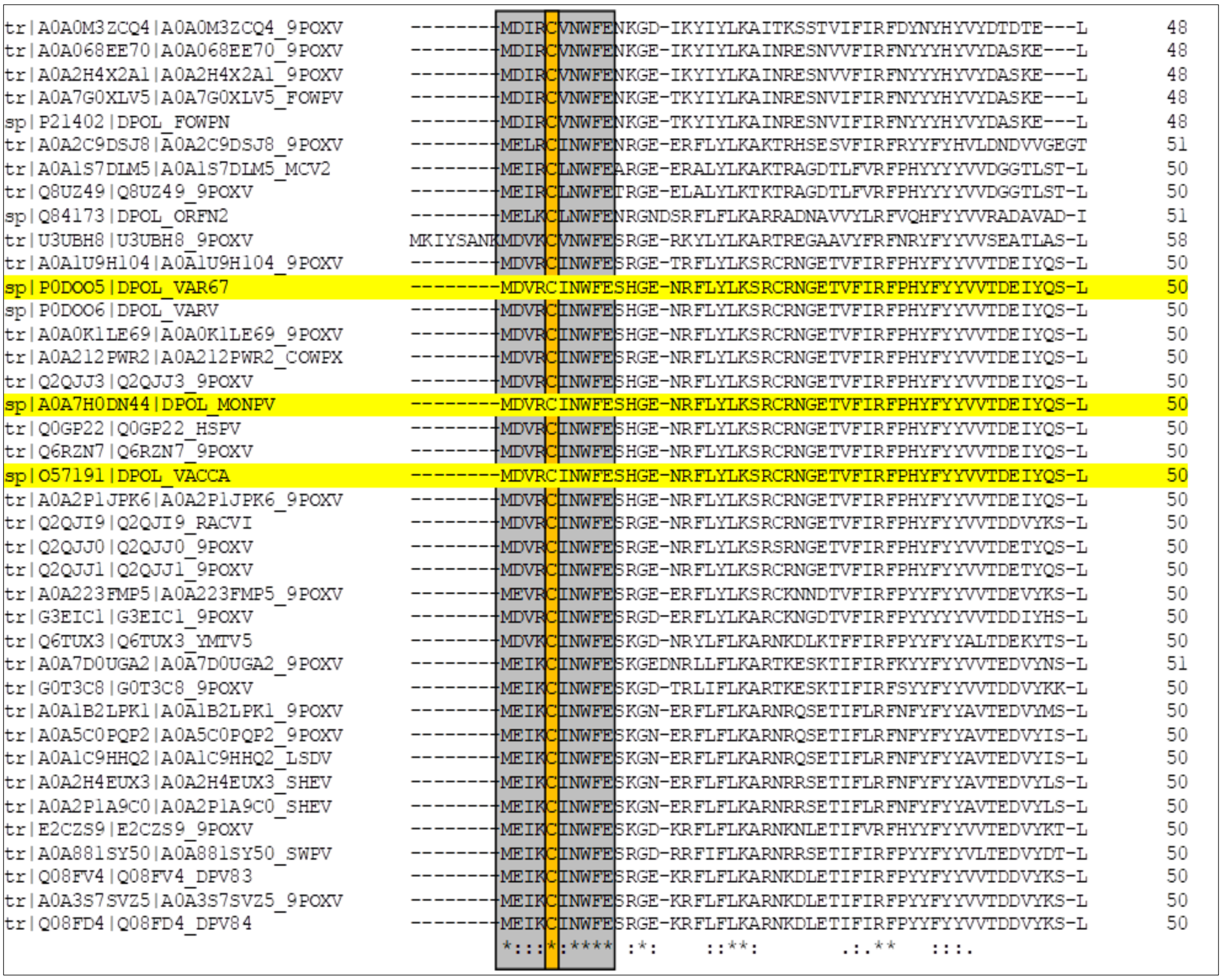
3.1. MSA Analysis of the replicative DNA Pol from Poxviruses

Figure 3 shows the MSA of the DNA pols from poxviruses belonging to different genera that infect both vertebrates and invertebrates (only the required regions for the discussions are shown). The variola, vaccinia and mpox viral DNA pol sequences are highlighted. The N-terminal region (NTD) (~160 amino acids) starts with a highly conserved decapeptide in all, in addition to a few invariant aromatic amino acids. This region is followed by a highly conserved PR exonuclease domain. The PR exonuclease domain contains the typical, completely conserved active site amino acids (highlighted in light blue) as found in other PR DNA pols. A ZBM connects the N-terminal and the PR exonuclease domains. Additionally, a consecutive Ns and a -KLDS- direct repeat are observed in the PR exonuclease domain (highlighted). The PR exonuclease domain is followed by the pol domain which is also highly conserved in all. Interestingly, the pol catalytic amino acids are completely conserved (highlighted in yellow) and in close agreement with other DNA pols reported from both pro- and eukaryotes. The two typical motifs, –SLYP**S**- and –YGDTDS- which are the characteristic of the B-family pols are found before and after the proposed pol active site, respectively (Table 3). However, a significant difference is observed in the last amino acid of the first pentapeptide motif in all poxviral pols where the usual S is replaced by an N (-SLYP**N**-) [37]. However, the second motif is completely conserved in all the poxviral DNA pols (highlighted) as reported in other B-family pols. Highly conserved Ds (highlighted in dark green) in the pol domain are implicated in the catalytic metal-binding.

Another marked difference observed between the human and poxviral replicative pols is the absence of the two regulatory ZBMs in their CTDs. For example, the catalytic subunits of all the three eukaryotic replicative DNA pols (pol α, ε and δ), contain two invariant ZBMs in their CTDs and they are named CysA and CysB. The CysA acts as the regular ZBM and binds a Zn^{2+} whereas the CysB binds a –[4Fe-4S]- cluster [38]. Another significant difference is that the CTDs of the poxviral DNA pols contain a–HNH- type of endonuclease motif -^{896}H**H**^{1}SNYKSADNP**N**^{11}MYLVTEY**N**^{8}- marked in bracket and also highlighted) (numbering with respect to mpox viral DNA pol).

The HNH endonuclease motif is a small nucleic acid-binding motif (~30 amino acids in length) found in all kingdoms of life and is particularly very common in the genomes of bacteria and their phages and also in organellar genomes. It contains the following three invariant amino acids, **-H-----N----H-** (where the last H is replaced by an N in some enzymes. However, the **–HNN-** motif functions in the same way as the **–HNH-** motif) (Fig. 4). The HNH endonucleases essentially involve in a metal ion-mediated cleavage of DNAs.

CLUSTAL O (1.2.4) MSA of the DNA polymerases from different poxviruses



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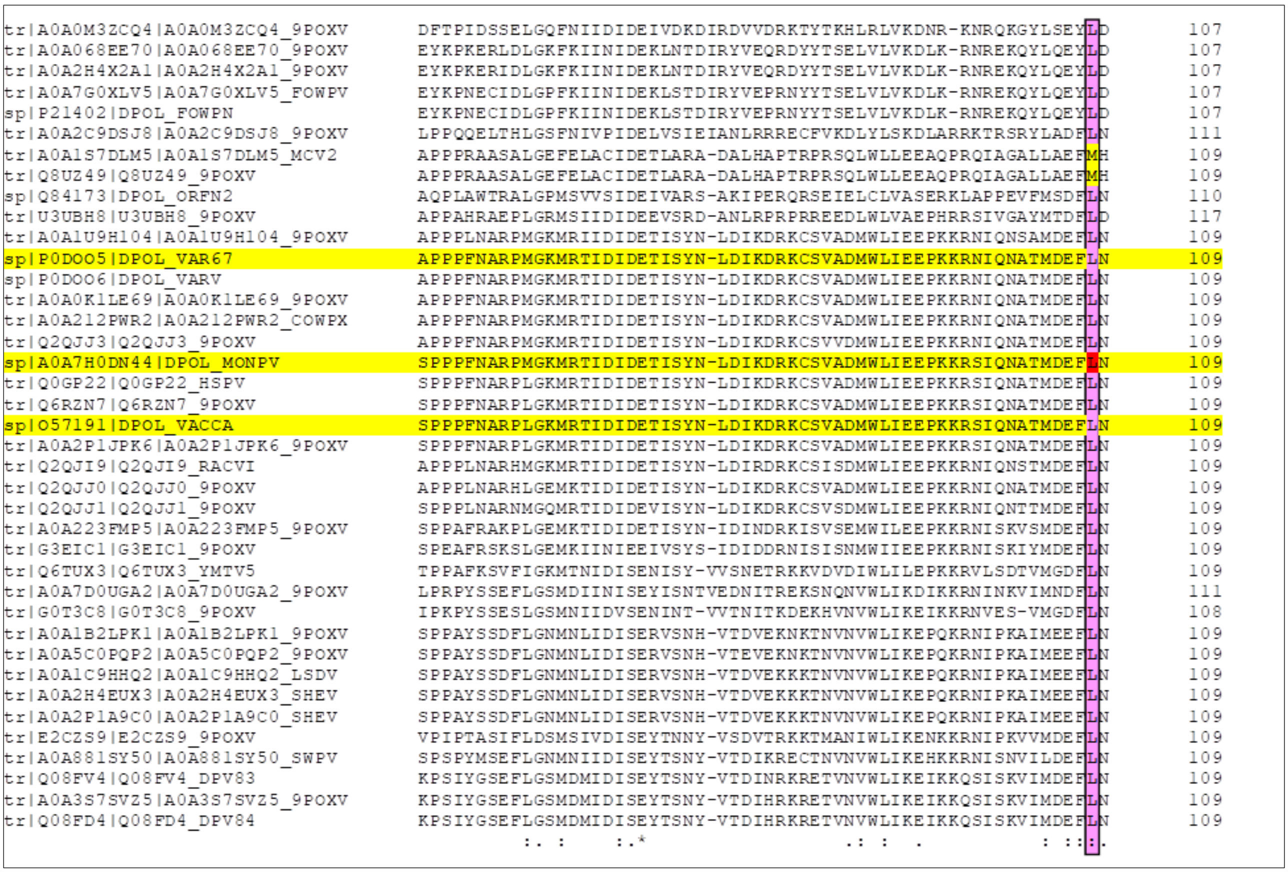

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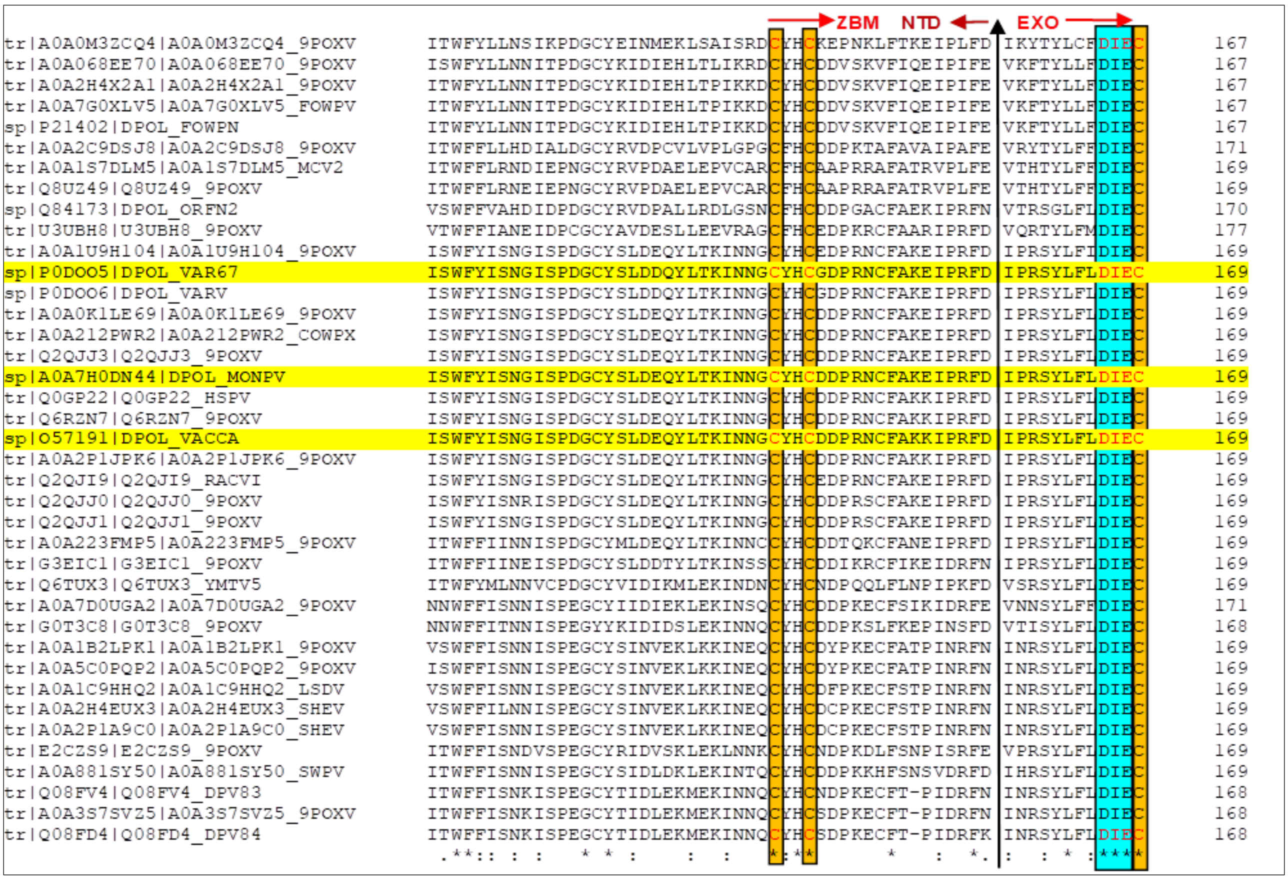

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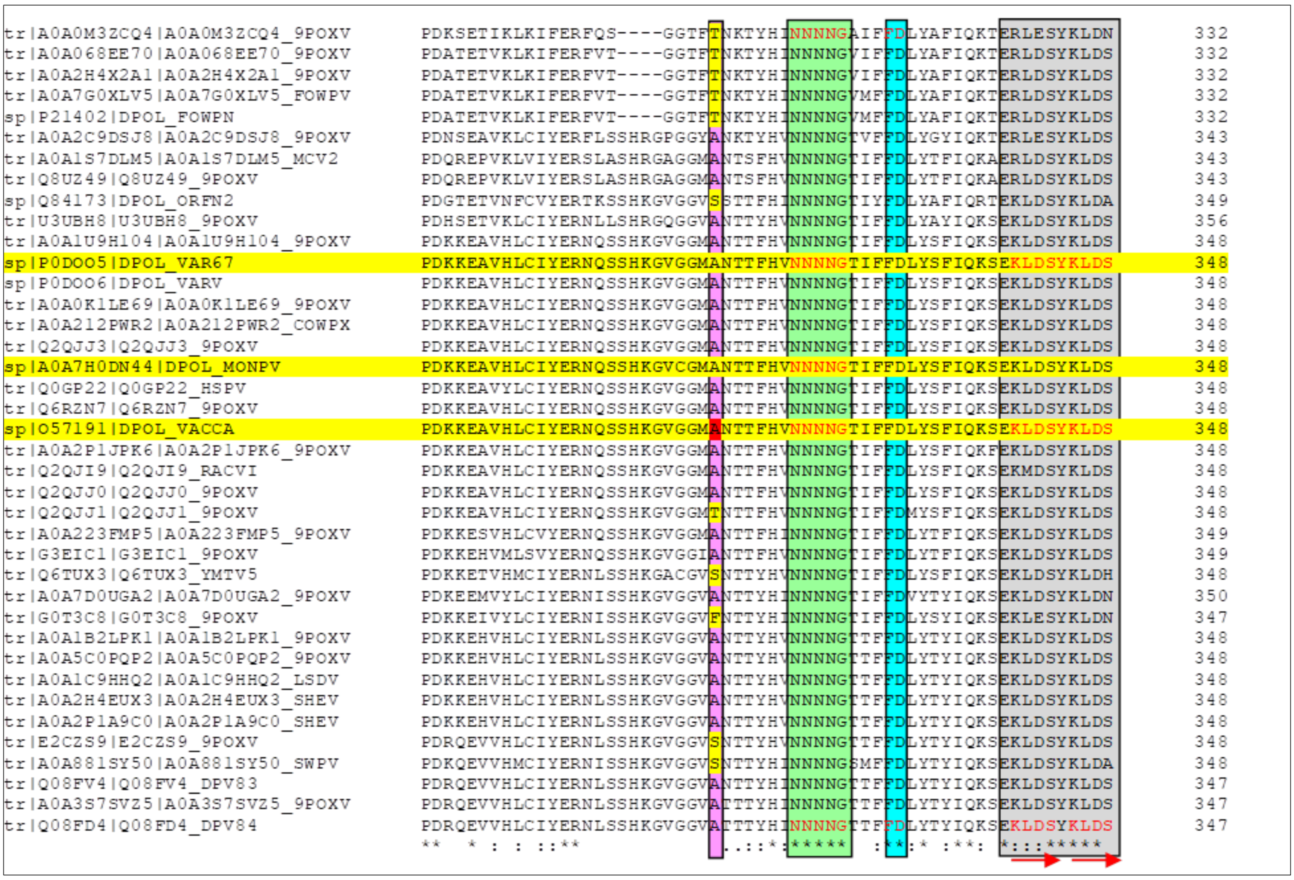

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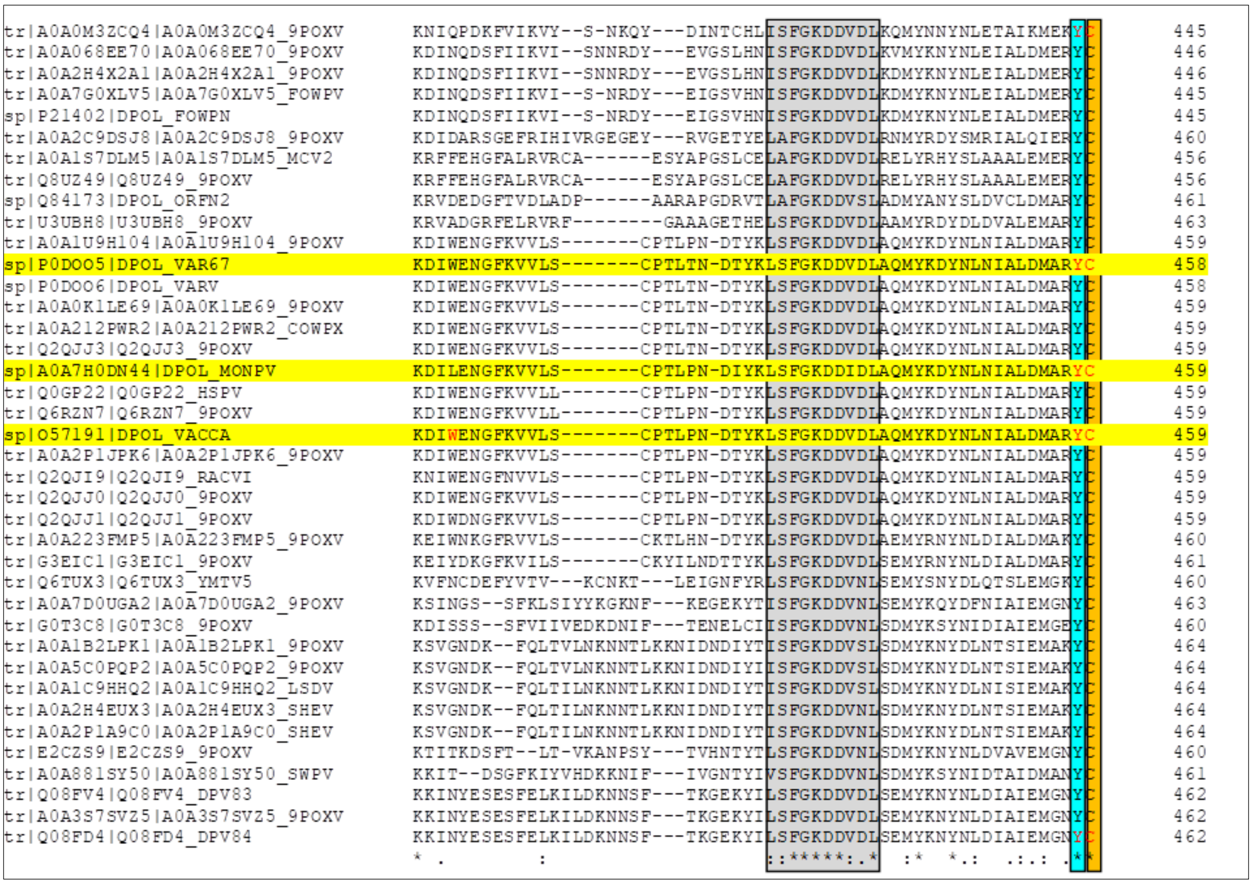

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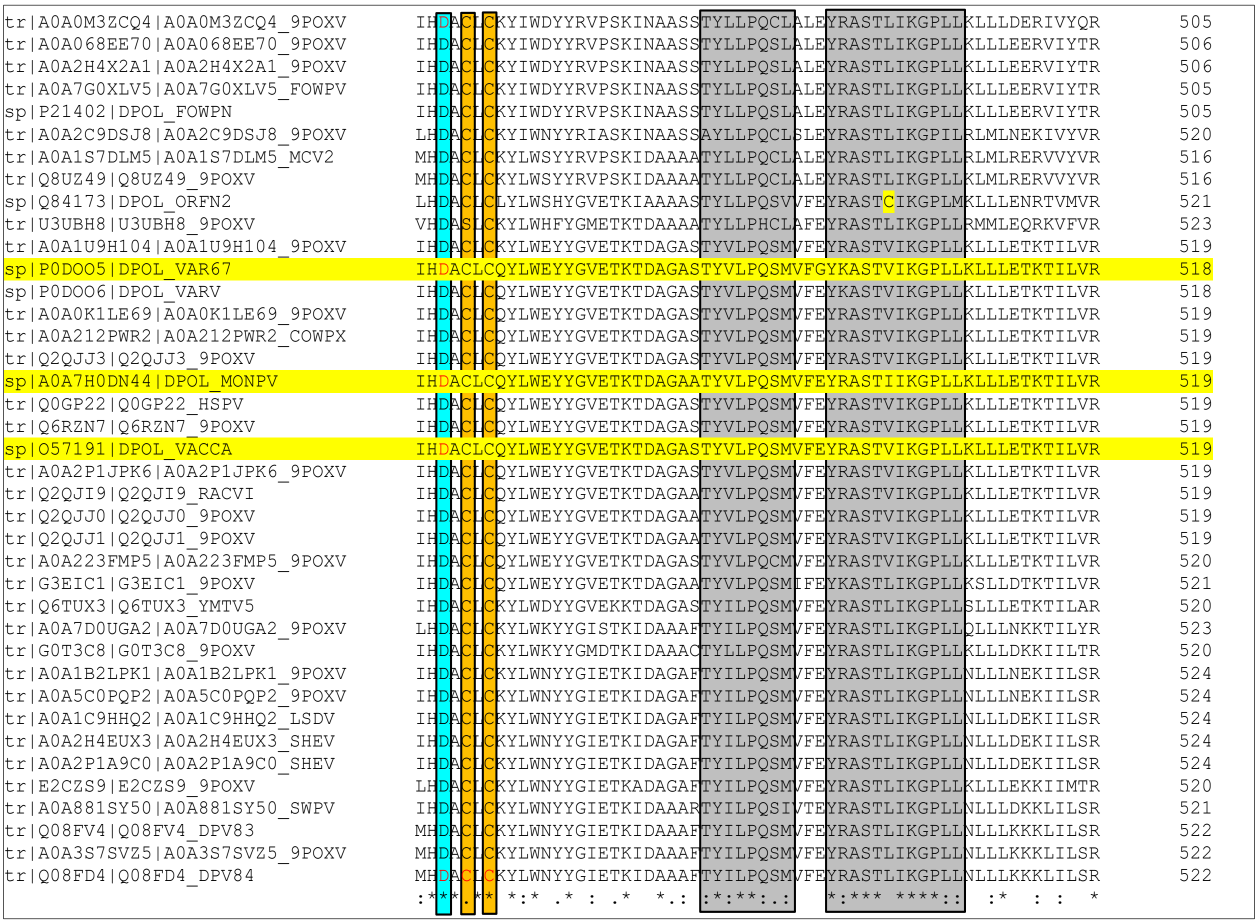

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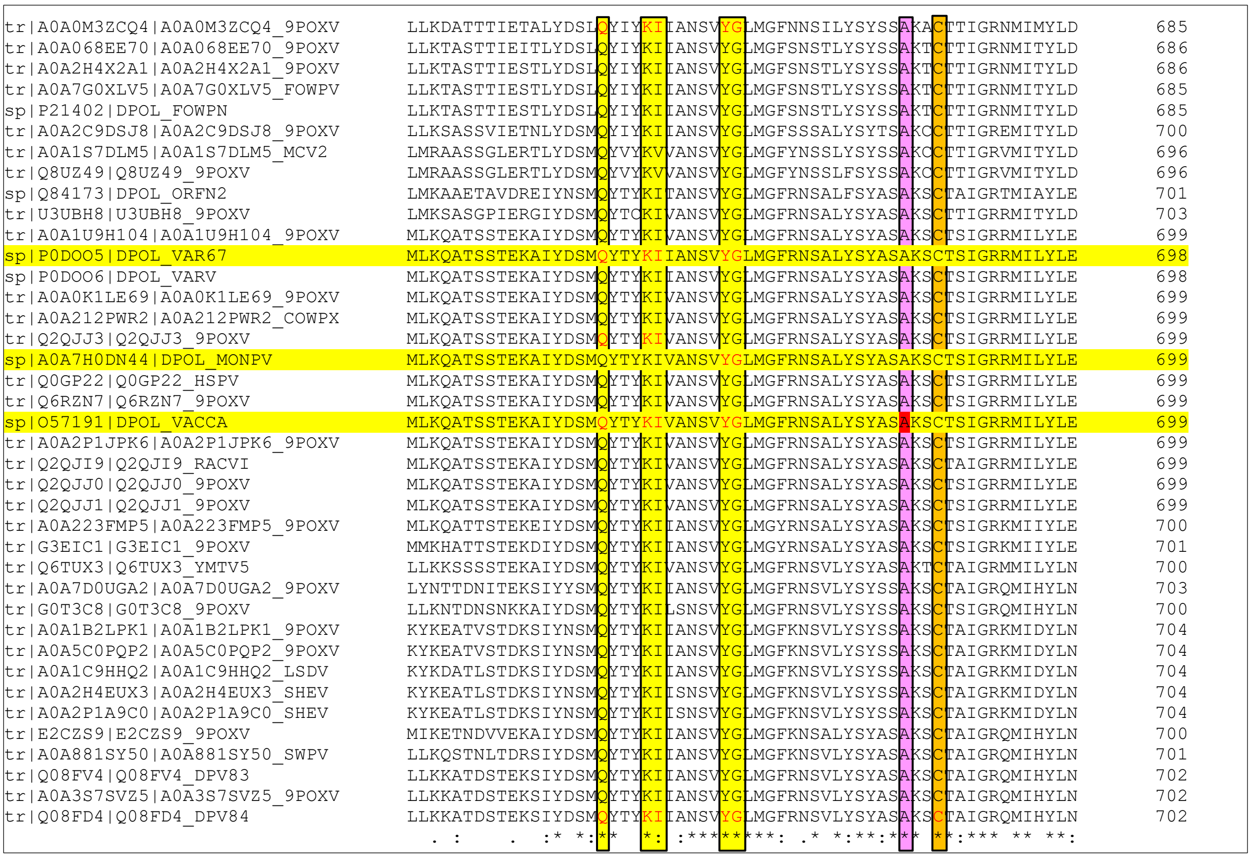

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tr|E2CZS9|E2CZS9_9POXV              MIKETNDVVEKAIYDSMQYTYKIIANSVYGLMGFKNSALYSYASAKSCTAIGRQMIHYLN     700
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tr|A0A3S7SVZ5|A0A3S7SVZ5_9POXV      LLKKATDSTEKSIYDSMQYTYKIIANSVYGLMGFRNSVLYSYASAKSCTAIGRQMIHYLN     702
tr|Q08FD4|Q08FD4_DPV84              LLKKATDSTEKSIYDSMQYTYKIIANSVYGLMGFRNSVLYSYASAKSCTAIGRQMIHYLN     702
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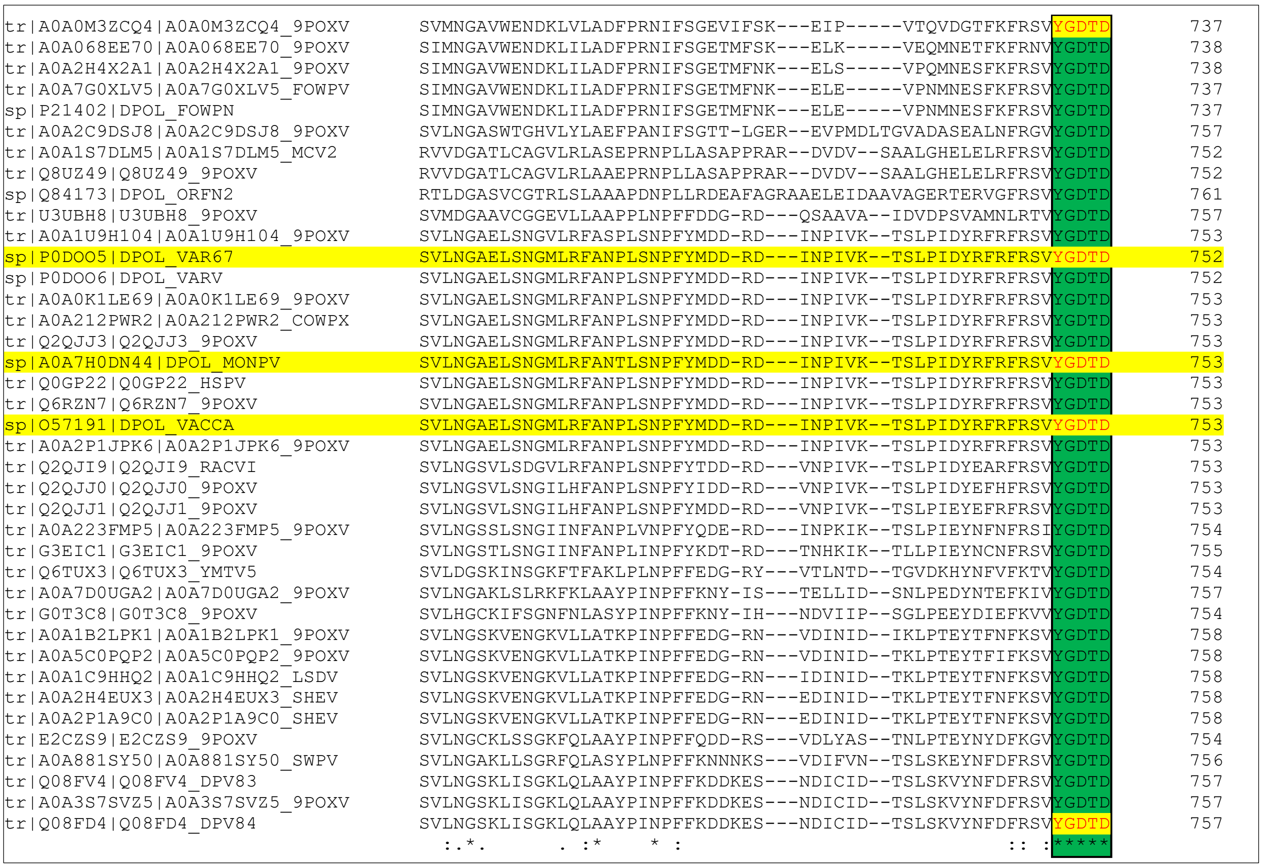

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tr|A0A068EE70|A0A068EE70_9POXV      SIMNGAVWENDKLILADFPRNIFSGETMFSK---ELK-----VEQMNETFKFRNVYGDTD       738
tr|A0A2H4X2A1|A0A2H4X2A1_9POXV      SIMNGAVWENDKLILADFPRNIFSGETMFNK---ELS-----VPQMNESFKFRSVYGDTD       738
tr|A0A7G0XLV5|A0A7G0XLV5_FOWPV      SIMNGAVWENDKLILADFPRNIFSGETMFNK---ELE-----VPNMNESFKFRSVYGDTD       737
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tr|A0A1S7DLM5|A0A1S7DLM5_MCV2       RVVDGATLCAGVLRLASEPRNPLLASAPPRAR--DVDV--SAALGHELELRFRSVYGDTD       752
tr|Q8UZ49|Q8UZ49_9POXV              RVVDGATLCAGVLRLAAEPRNPLLASAPPRAR--DVDV--SAALGHELELRFRSVYGDTD       752
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tr|U3UBH8|U3UBH8_9POXV              SVMDGAAVCGGEVLLAAPPLNPFFDDG-RD---QSAAVA--IDVDPSVAMNLRTVYGDTD       757
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sp|P0DOO5|DPOL_VAR67                SVLNGAELSNGMLRFANPLSNPFYMDD-RD---INPIVK--TSLPIDYRFRFRSVYGDTD       752
sp|P0DOO6|DPOL_VARV                 SVLNGAELSNGMLRFANPLSNPFYMDD-RD---INPIVK--TSLPIDYRFRFRSVYGDTD       752
tr|A0A0K1LE69|A0A0K1LE69_9POXV      SVLNGAELSNGMLRFANPLSNPFYMDD-RD---INPIVK--TSLPIDYRFRFRSVYGDTD       753
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tr|A0A5C0PQP2|A0A5C0PQP2_9POXV      SVLNGSKVENGKVLLATKPINPFFEDG-RN---VDINID--TKLPTEYTFIFKSVYGDTD       758
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tr|A0A1S7DLM5|A0A1S7DLM5_MCV2       LEVDLFAE FAARAQPLEMFLLSRLHHRNYKAPDNPNVELVNRYNRENLEPIELGERYYYA       930
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tr|A0A5C0PQP2|A0A5C0PQP2_9POXV      LESDLQIE FETKTAPLDMFLLSRTHHCNYKSSDNPNMYLVNEYNKNNDEIIEIGERYYFA       936
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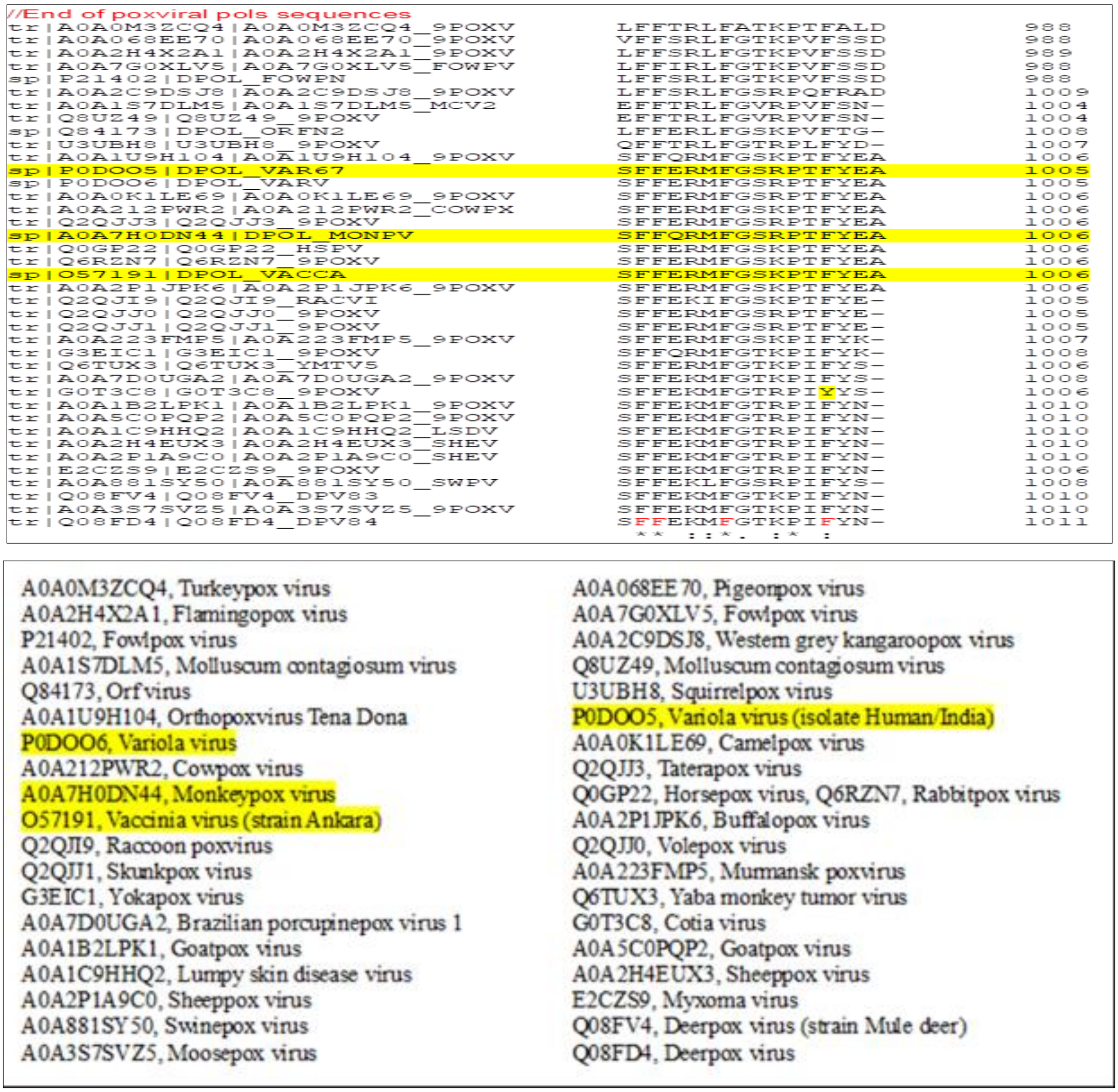

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tr|Q8UZ49|Q8UZ49_9POXV              EFFTRLFGVRPVFSN-      1004
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tr|U3UBH8|U3UBH8_9POXV              QFFTRLFGTRPLFYD-      1007
tr|A0A1U9H104|A0A1U9H104_9POXV      SFFQRMFGSKPTFYEA      1006
sp|P0DOO5|DPOL_VAR67                SFFERMFGSRPTFYEA      1005
sp|P0DOO6|DPOL_VARV                 SFFERMFGSRPTFYEA      1005
tr|A0A0K1LE69|A0A0K1LE69_9POXV      SFFERMFGSRPTFYEA      1006
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tr|G0T3C8|G0T3C8_9POXV              SFFEKMFGTRPIYYS-      1006
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tr|A0A881SY50|A0A881SY50_SWPV       SFFEKLFGSRPIFYS-      1008
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tr|A0A3S7SVZ5|A0A3S7SVZ5_9POXV      SFFEKMFGTKPIFYN-      1010
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                                     ** ::*. :* :
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A0A0M3ZCQ4, Turkeypox virus
A0A2H4X2A1, Flamingopox virus
P21402, Fowlpox virus
A0A1S7DLM5, Molluscum contagiosum virus
Q84173, Orf virus
A0A1U9H104, Orthopoxvirus Tena Dona
P0DOO6, Variola virus
A0A212PWR2, Cowpox virus
A0A7H0DN44, Monkeypox virus
O57191, Vaccinia virus (strain Ankara)
Q2QJI9, Raccoon poxvirus
Q2QJJ1, Skunkpox virus
G3EIC1, Yokapox virus
A0A7D0UGA2, Brazilian porcupinepox virus 1
A0A1B2LPK1, Goatpox virus
A0A1C9HHQ2, Lumpy skin disease virus
A0A2P1A9C0, Sheeppox virus
A0A881SY50, Swinepox virus
A0A3S7SVZ5, Moosepox virus

A0A068EE70, Pigeonpox virus
A0A7G0XLV5, Fowlpox virus
A0A2C9DSJ8, Western grey kangaroopox virus
Q8UZ49, Molluscum contagiosum virus
U3UBH8, Squirrelpox virus
P0DOO5, Variola virus (isolate Human/India)
A0A0K1LE69, Camelpox virus
Q2QJJ3, Taterapox virus
Q0GP22, Horsepox virus, Q6RZN7, Rabbitpox virus
A0A2P1JPK6, Buffalopox virus
Q2QJJ0, Volepox virus
A0A223FMP5, Murmansk poxvirus
Q6TUX3, Yaba monkey tumor virus
G0T3C8, Cotia virus
A0A5C0PQP2, Goatpox virus
A0A2H4EUX3, Sheeppox virus
E2CZS9, Myxoma virus
Q08FV4, Deerpox virus (strain Mule deer)
Q08FD4, Deerpox virus

Figure 3 MSA of different poxviral replicative DNA polymerase catalytic subunits

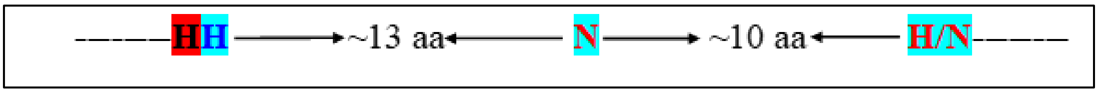


Figure 4 Structure of HNH endonuclease motif showing the invariant active site amino acids and the approximate distances between them

HNH motif has been identified in hundreds of prokaryotic and eukaryotic organisms and is known to involve in many important functions like, DNA homing, restriction, repair, chromosome degradation, etc. One of the main functions of these endonucleases is to promote the lateral transfer of their own coding and flanking DNA regions between genomes, by a recombination-dependent process known as 'homing'. Importantly, unlike restriction enzymes, these homing endonucleases have a very long recognition sequence of ~20 amino acids to prevent random cleaving of the host genome. Some of the -HNH- motifs are free-standing and some are embedded in other genes [39].

The poxviral DNA pol apoenzyme with its processive factor and UDG form the active holoenzyme (Figs. 1A & 1B). The structure of the holoenzyme from the mpox virus has been extensively studied by cryo-EM technique by Peng *et al.* [27]

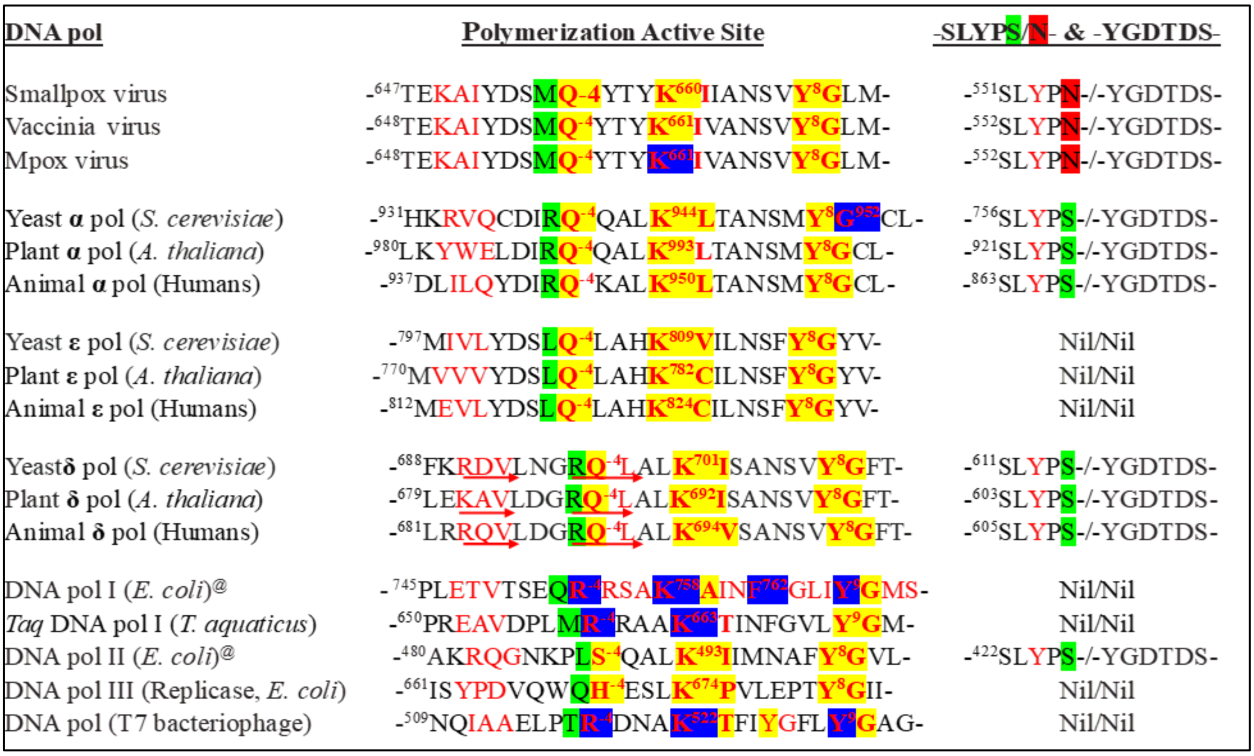
and Wang *et al*. [28]. They found that the D^{549} and D^{753}, together with the triphosphate tail of dTTP coordinated one divalent metal ion, possibly the catalytic Mg^{2+} (highlighted in dark green). Therefore, the two invariant Ds, viz. D^{549} and D^{753} of poxviral DNA pols could be equivalent to the two invariant Ds (D^{705} and D^{882}) which coordinate β- and γ-phosphates of the incoming dNTP in the DNA pol I of *E. coli* [40]. Furthermore, Peng *et al*. [27] found the ribose of dTTP stacks on top of the phenyl ring of Y^{554} from the palm domain, which is critical to discriminating against ribonucleotides by providing a steric hindrance to the ribonucleotide-specific 2'-OH. Interestingly, the present MSA analysis locates that the base discriminating amino acid Y^{554} in one of the characteristic motifs, –SL**Y**$^{\mathbf{554}}$PN-, found in the poxvirus DNA pols including the mpox, variola and vaccinia and also found in other B-family pols [37]. The positively charged R^{634} and K^{661} of the fingers' domain are found closer to the active site, where they could interact with the triphosphate group of incoming dNTPs. In fact, the K^{661} is found in the proposed mpox, variola and vaccinia viral DNA pol active sites, **-**^{656}M**Q**$^{\mathbf{-4}}$YTY**K**$^{\mathbf{661}}$IVANSV**Y**$^{\mathbf{8}}$**G**L**-** (Table 3) and proposed as the proton abstractor to initiate the catalysis. Table 3 shows the similarity among the DNA pol active sites of the replicative pols from both pro- and eukaryotes.

It is suggested that some crucial mutations in viral proteins may alter the phenotype and pathogenicity of the viral strains. The F8L mutation (L^{108}→F) which emerged in 2022, is suggested to be a potential contributing factor to the 2022 mpox outbreak (highlighted in light magenta). The present analysis shows that the L^{108}→F mutton is located in the NTD (not in the PR exonuclease or pol domains) of the mpox virus DNA pol and conserved in most of the poxviral pols with few exceptions and hence, possibly involve with its interaction with the proccessivity factor. Similarly, the CDV resistance observed in VACV DNA pol is achieved by A^{314}→T and A^{684}→V mutations in E9 DNA pol catalytic subunit. Both A^{314} and A^{684} are conserved in mpox virus also. The present study identifies the VACV pol mutation, A^{314}→T within the PR exonuclease domain (highlighted in light magenta) and interestingly, is not conserved in all poxviral DNA pols. However, the second mutation, A^{684}→V is completely conserved in all poxvirus DNA pols including the mpox virus (highlighted in light magenta) and is located downstream of the pol catalytic core. These results suggest that these mutations do not alter any of the active site amino acids in the PR exonuclease and pol domains, but by simply altering the residues close to the active sites of the enzyme, block the binding of the DNA pol inhibitor, CDV, and make the virus resistant to CDV. Kannan *et al*. [41] have suggested that the A^{314}→T mutation could interfere with the shuttling of primer to the PR exonuclease domain (as it is located within the PR exonuclease domain), whereas A^{684}→V is likely to interfere with template positioning (as it is located in the 'palm' subdomain), which could alter the CDV-pp binding at the dCTP-binding pocket.

3.2. Conservation of the polymerase catalytic core region

Table 3 shows a detailed analysis of the polymerization active site core regions of different pols from bacteria, bacteriophages, smallpox, vaccinia, mpox viruses, yeast, plant and animal. The polymerization active site amino acids are arrived at both from the sequence similarities and from the experimentally confirmed ones (highlighted in dark blue). High similarity among the pol catalytic cores suggests that most of the nucleotide pols not only share a common 3D structure of their pol domains (exhibiting palm, fingers and thumb subdomains), but also very similar catalytic core. It is clear from the table that the A-family (Pol I) and C-family (Pol III) DNA pols do not possess the -SLYPS- and -YGDTDS motifs and only the B-family pols possess the two invariant motifs. It is interesting to note that even among the B-family pols, the ε pols from different sources also do not possess these two characteristic motifs (Table 3).

Table 3 Polymerase active site catalytic core regions and presence/absence of SYLPS/N and YGDTDS motifs in DNA pols from smallpox, vaccinia, mpox viruses and plant, animal, bacteria and bacteriophages



DNA pol	Polymerization Active Site	-SLYPS/N- & -YGDTDS-
Smallpox virus	-^{647}TEKAIYDSMQ-4YTYK^{660}IIANSVY^{8}GLM-	-^{551}SLYPN-/-YGDTDS-
Vaccinia virus	-^{648}TEKAIYDSMQ^{-4}YTYK^{661}IVANSVY^{8}GLM-	-^{552}SLYPN-/-YGDTDS-
Mpox virus	-^{648}TEKAIYDSMQ^{-4}YTYK^{661}IVANSVY^{8}GLM-	-^{552}SLYPN-/-YGDTDS-
Yeast **α** pol (*S. cerevisiae*)	-^{931}HKRVQCDIRQ^{-4}QALK^{944}LTANSMY^{8}G^{952}CL-	-^{756}SLYPS-/-YGDTDS-
Plant **α** pol (*A. thaliana*)	-^{980}LKYWELDIRQ^{-4}QALK^{993}LTANSMY^{8}GCL-	-^{921}SLYPS-/-YGDTDS-
Animal **α** pol (Humans)	-^{937}DLILQYDIRQ^{-4}KALK^{950}LTANSMY^{8}GCL-	-^{863}SLYPS-/-YGDTDS-
Yeast ε pol (*S. cerevisiae*)	-^{797}MIVLYDSLQ^{-4}LAHK^{809}VILNSFY^{8}GYV-	Nil/Nil
Plant ε pol (*A. thaliana*)	-^{770}MVVVYDSLQ^{-4}LAHK^{782}CILNSFY^{8}GYV-	Nil/Nil
Animal ε pol (Humans)	-^{812}MEVLYDSLQ^{-4}LAHK^{824}CILNSFY^{8}GYV-	Nil/Nil
Yeast**δ** pol (*S. cerevisiae*)	-^{688}FKRDVLNGRQ^{-4}LALK^{701}ISANSVY^{8}GFT-	-^{611}SLYPS-/-YGDTDS-
Plant **δ** pol (*A. thaliana*)	-^{679}LEKAVLDGRQ^{-4}LALK^{692}ISANSVY^{8}GFT-	-^{603}SLYPS-/-YGDTDS-
Animal **δ** pol (Humans)	-^{681}LRRQVLDGRQ^{-4}LALK^{694}VSANSVY^{8}GFT-	-^{605}SLYPS-/-YGDTDS-
DNA pol I (*E. coli*)@	-^{745}PLETVTSEQR^{-4}RSAK^{758}AINF^{762}GLIY^{9}GMS-	Nil/Nil
Taq DNA pol I (*T. aquaticus*)	-^{650}PREAVDPLMR^{-4}RAAK^{663}TINFGVLY^{9}GM-	Nil/Nil
DNA pol II (*E. coli*)@	-^{480}AKRQGNKPLS^{-4}QALK^{493}IIMNAFY^{8}GVL-	-^{422}SLYPS-/-YGDTDS-
DNA pol III (Replicase, *E. coli*)	-^{661}ISYPDVQWQH^{-4}ESLK^{674}PVLEPTY^{8}GII-	Nil/Nil
DNA pol (T7 bacteriophage)	-^{509}NQIAAELPTR^{-4}DNAK^{522}TFIYGFLY^{9}GAG-	Nil/Nil

@ DNA pol I and II are not the replicative pols, but only the pol II possesses the two typical conserved motifs, -SLYPS- and –YGDTDS- suggesting possible different evolutionary origins. However, these two motifs are not also found in the replicative pol III of *E. coli* and eukaryotic replicative **ε** pols.

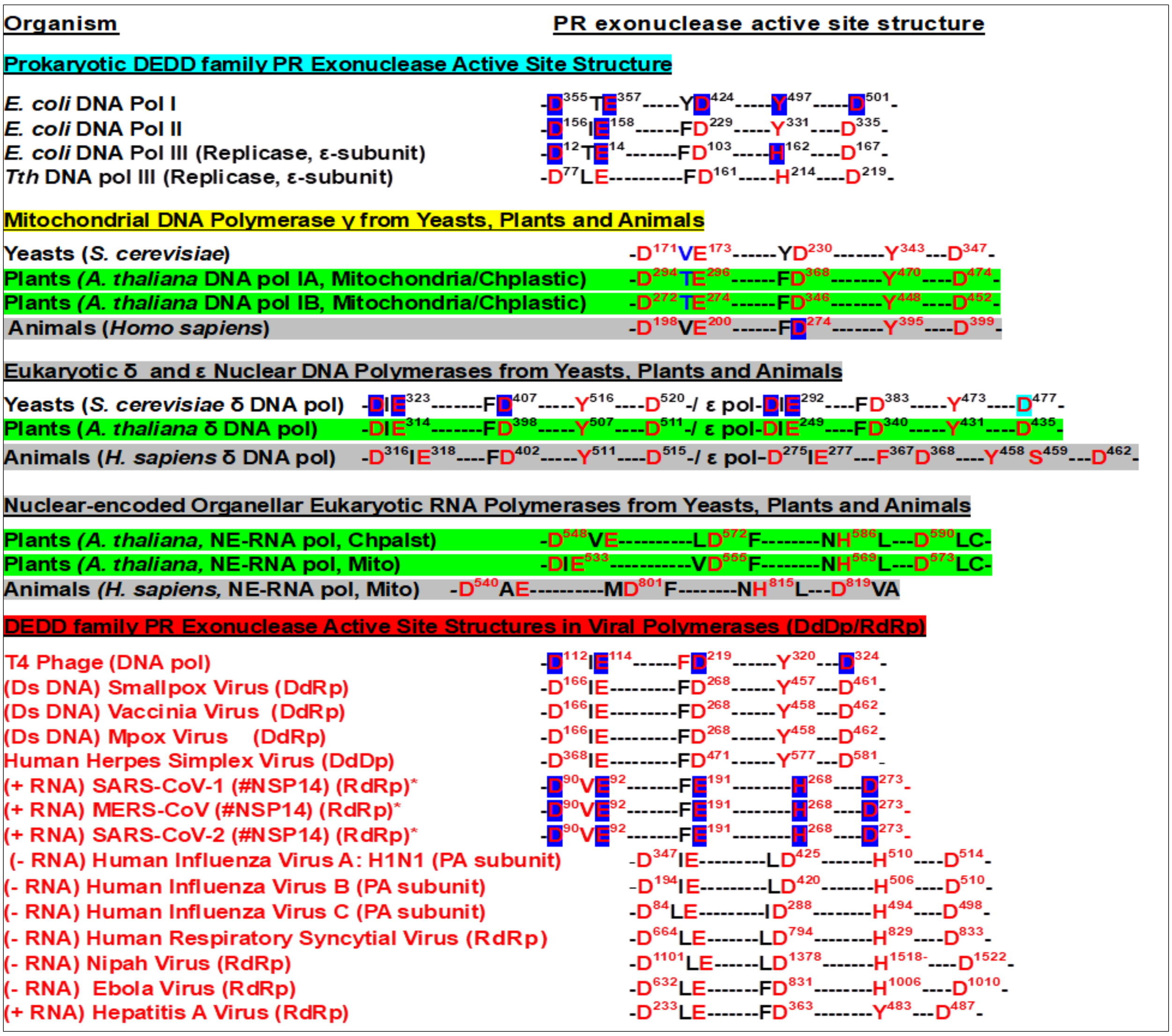
The confirmed active site amino acids (by SDM and active site-directed labelling) are highlighted in dark blue. In the *E. coli* pol I, the replacement of K^{758} with A^{758} caused a 1,000-fold reduction in k_{cat}. In *Taq* pol I, R^{659} and K^{663} were immutable [42].

The Ala substitutions in the *E. coli* pol I resulted in moderate to severe effects on the pol I activity of the individual mutant enzymes. Severe loss of activity was associated with R^{754}→A, K^{758}→A, F^{762}→A, and Y^{766}→A (highlighted in dark blue) [43].

3.3. Conservation of PR exonuclease active site domain in DNA polymerases

DNA replicases replicate the genomes with very high fidelity. However, during their incredibly high-speed polymerization reactions (~100 nt in eukaryotes to ~1000 nt in prokaryotes per second), mistakes do happen and the pols sometimes insert the wrong nucleotide or sometimes skip a nucleotide or add a nucleotide into the sequence. Almost all of these mistakes are fixed meticulously through different DNA repair enzymes associated with genome replications. For example, most of the mistakes are corrected immediately during the replication process itself through the PR exonucleases associated or part of the DNA replicases.

Table 4 DEDD-superfamily of PR exonuclease active site amino acids of the replicative DNA pols from viral and pro- and eukaryotic sources



Organism	PR exonuclease active site structure
Prokaryotic DEDD family PR Exonuclease Active Site Structure	
E. coli DNA Pol I	-D^{355}TE^{357}-----YD^{424}-----Y^{497}-----D^{501}-
E. coli DNA Pol II	-D^{156}IE^{158}------FD^{229}-----Y^{331}----D^{335}-
E. coli DNA Pol III (Replicase, ε-subunit)	-D^{12}TE^{14}-------FD^{103}-----H^{162}----D^{167}-
Tth DNA pol III (Replicase, ε-subunit)	-D^{77}LE----------FD^{161}-----H^{214}----D^{219}-
Mitochondrial DNA Polymerase γ from Yeasts, Plants and Animals	
Yeasts (*S. cerevisiae*)	-D^{171}VE^{173}------YD^{230}-------Y^{343}---D^{347}-
Plants *(A. thaliana* DNA pol IA, Mitochondria/Chplastic)	-D^{294}TE^{296}------FD^{368}-------Y^{470}----D^{474}-
Plants *(A. thaliana* DNA pol IB, Mitochondria/Chplastic)	-D^{272}TE^{274}------FD^{346}-------Y^{448}----D^{452}-
Animals (*Homo sapiens*)	-D^{198}VE^{200}------FD^{274}-------Y^{395}----D^{399}-
Eukaryotic δ and ε Nuclear DNA Polymerases from Yeasts, Plants and Animals	
Yeasts (*S. cerevisiae* δ DNA pol)	-DIE^{323}-------FD^{407}-----Y^{516}----D^{520}-/ ε pol-DIE^{292}----FD^{383}-----Y^{473}----D^{477}-
Plants (*A. thaliana* δ DNA pol)	-DIE^{314}-------FD^{398}-----Y^{507}----D^{511}-/ ε pol-DIE^{249}----FD^{340}-----Y^{431}----D^{435}-
Animals (*H. sapiens* δ DNA pol)	-D^{316}IE^{318}----FD^{402}-----Y^{511}----D^{515}-/ ε pol-D^{275}IE^{277}---F^{367}D^{368}----Y^{458} S^{459}---D^{462}-
Nuclear-encoded Organellar Eukaryotic RNA Polymerases from Yeasts, Plants and Animals	
Plants *(A. thaliana,* NE-RNA pol, Chpalst)	-D^{548}VE----------LD^{572}F--------NH^{586}L---D^{590}LC-
Plants *(A. thaliana,* NE-RNA pol, Mito)	-DIE^{533}-----------VD^{555}F--------NH^{569}L---D^{573}LC-
Animals *(H. sapiens,* NE-RNA pol, Mito)	-D^{540}AE----------MD^{801}F--------NH^{815}L---D^{819}VA
DEDD family PR Exonuclease Active Site Structures in Viral Polymerases (DdDp/RdRp)	
T4 Phage (DNA pol)	-D^{112}IE^{114}------FD^{219}------Y^{320}---D^{324}-
(Ds DNA) Smallpox Virus (DdRp)	-D^{166}IE---------FD^{268}------Y^{457}---D^{461}-
(Ds DNA) Vaccinia Virus (DdRp)	-D^{166}IE---------FD^{268}------Y^{458}---D^{462}-
(Ds DNA) Mpox Virus (DdRp)	-D^{166}IE---------FD^{268}------Y^{458}---D^{462}-
Human Herpes Simplex Virus (DdDp)	-D^{368}IE---------FD^{471}------Y^{577}---D^{581}-
(+ RNA) SARS-CoV-1 (#NSP14) (RdRp)*	-D^{90}VE^{92}-------FE^{191}---------H^{268}----D^{273}-
(+ RNA) MERS-CoV (#NSP14) (RdRp)*	-D^{90}VE^{92}-------FE^{191}---------H^{268}----D^{273}-
(+ RNA) SARS-CoV-2 (#NSP14) (RdRp)*	-D^{90}VE^{92}-------FE^{191}---------H^{268}----D^{273}-
(- RNA) Human Influenza Virus A: H1N1 (PA subunit)	-D^{347}IE---------LD^{425}-------H^{510}----D^{514}-
(- RNA) Human Influenza Virus B (PA subunit)	-D^{194}IE---------LD^{420}-------H^{506}----D^{510}-
(- RNA) Human Influenza Virus C (PA subunit)	-D^{84}LE---------ID^{288}--------H^{494}----D^{498}-
(- RNA) Human Respiratory Syncytial Virus (RdRp)	-D^{664}LE-------LD^{794}--------H^{829}----D^{833}-
(- RNA) Nipah Virus (RdRp)	-D^{1101}LE------LD^{1378}-------H^{1518-}----D^{1522}-
(- RNA) Ebola Virus (RdRp)	-D^{632}LE-------FD^{831}--------H^{1006}----D^{1010}-
(+ RNA) Hepatitis A Virus (RdRp)	-D^{233}LE-------FD^{363}--------Y^{483}---D^{487}-

Eukaryotic replicative α pols (DNA primases) lack the PR exo active site.

Tth, *Thermus thermophilus*; NE, Nuclear encoded; Chplast, Chloroplast; Mito, Mitochondria;

The confirmed PR exo active site amino acids (by SDM and Crystallography) are highlighted in dark blue/light blue, respectively.;

*All possess the same PR exonuclease domain and their active site amino acids are completely conserved in Bat-RaTG13, Pangolin, Civet, SARS-CoV-1, MERS-CoV, SARS-CoV2 and HCoV-NL63.

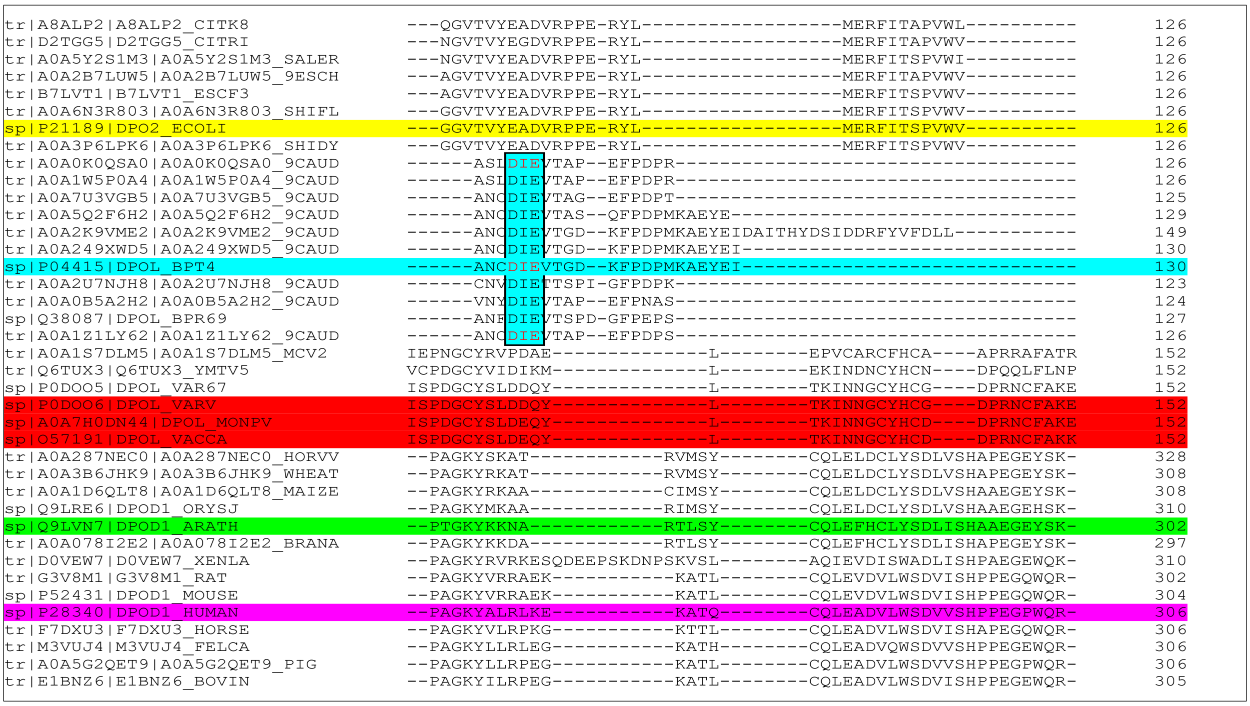
#NSP14 is a multifunctional enzyme with two distinct activities, an N-terminal 3'→5' exoribonuclease (ExoN) and a C-terminal N7-methyltransferase (N7-MTase), both are crucial for lifecycle of the coronaviruses, indicating NSP14 as one of the prominent targets for the development of antiviral drugs.

In DNA replicases a wrong addition stalls the pol and the PR exonuclease active site moves in and removes the wrong nucleotide and allowing the pol to proceed. Thus, the PR exo and pol activities undergo polymerase-to-exonuclease and exonuclease-to-polymerase active site switching during the replication process without having the DNA pol to be disassociated from template DNA every time. The rest of the mistakes are corrected by a process known as mismatch repair after the replication. The incorrectly base-paired nucleotides cause deformities in the secondary structure of the final DNA molecule. The mismatch repair enzymes recognize these deformities and fix them by removing the incorrectly paired nucleotide and replacing it with the correct nucleotide. However, some replication errors make it past these repair mechanisms and thus, become permanent mutations. Such altered nucleotide sequences can then be passed down from one generation to the next, if they occur in cells that give rise to gametes. When the genes for the DNA repair enzymes themselves become mutated, replication mistakes begin accumulating at an alarmingly higher rate and such mutations can lead to many types of cancer in animals. It should also be noted that if the DNA repair were perfect and no mutations ever accumulated, there would be no genetic variation(s) and, in fact, these variations serve as the basis for the evolution of new variants. Table 4 shows the conservation of the PR exonuclease active site amino acids from viruses to animals and plants. These PR exonucleases are classified under –DEDD- superfamily of exonucleases and they use either an Y or H as a proton acceptor from the metal-activated water molecule in the active site during the PR reactions [40].

3.4. 'Mix and Match' MSA of the replicative pols from 5 different sources, viz. bacteria, bacteriophages, poxviruses, plants and animals

Figure 5 shows the 'mix and match' MSA analysis of various replicative pols. The replicative pols analyzed include from 5 different sources, viz. bacteria, bacteriophages, poxviruses, plants and animals and are highlighted in different colours. Interestingly, they revealed both similarities and differences between them. The N-terminal regions are not aligned and show lots of gaps indicating poor conservations among them. Even the first completely conserved triad -DIE- of the PR exonuclease domain is also not aligned in all, i.e., the distance conservation is not maintained between bacteria and bacteriophages and the rest. However, the next three PR exonuclease active site amino acids are completely conserved and aligned in all (highlighted). In contrast, the active site amino acids in the pol domain are almost completely conserved and aligned in all. Interestingly, all the three catalytic Ds in the pol domain are completely conserved in all pols (highlighted in dark green). The proposed, highly conserved –HNH- endonuclease motif is found only in the poxvirus DNA pols (highlighted), making the poxviral pols different from others. Similarly, the characteristic regulatory ZBMs invariably found at the CTDs of the eukaryotic replicative pols (α, δ and ε) are found only in plant and animal replicative pols (highlighted) and not in poxviral pols.

CLUSTAL O (1.2.4) Mix and Match MSA analysis of the replicative DNA pols from bacteriophages, bacteria, poxviruses, plants and animals.



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tr|A8ALP2|A8ALP2_CITK8              ---QGVTVYEADVRPPE-RYL------------------MERFITAPVWL----------       126
tr|D2TGG5|D2TGG5_CITRI              ---NGVTVYEGDVRPPE-RYL------------------MERFITAPVWV----------       126
tr|A0A5Y2S1M3|A0A5Y2S1M3_SALER      ---NGVTVYEADVRPPE-RYL------------------MERFITSPVWI----------       126
tr|A0A2B7LUW5|A0A2B7LUW5_9ESCH      ---AGVTVYEADVRPPE-RYL------------------MERFITAPVWV----------       126
tr|B7LVT1|B7LVT1_ESCF3              ---AGVTVYEADVRPPE-RYL------------------MERFITSPVWV----------       126
tr|A0A6N3R803|A0A6N3R803_SHIFL      ---GGVTVYEADVRPPE-RYL------------------MERFITSPVWV----------       126
sp|P21189|DPO2_ECOLI                ---GGVTVYEADVRPPE-RYL------------------MERFITSPVWV----------       126
tr|A0A3P6LPK6|A0A3P6LPK6_SHIDY      ---GGVTVYEADVRPPE-RYL------------------MERFITSPVWV----------       126
tr|A0A0K0QSA0|A0A0K0QSA0_9CAUD      ------ASLDIEVTAP--EFPDPR------------------------------------       126
tr|A0A1W5P0A4|A0A1W5P0A4_9CAUD      ------ASLDIEVTAP--EFPDPR------------------------------------       126
tr|A0A7U3VGB5|A0A7U3VGB5_9CAUD      ------ANCDIEVTAG--EFPDPT------------------------------------       125
tr|A0A5Q2F6H2|A0A5Q2F6H2_9CAUD      ------ANCDIEVTAS--QFPDPMKAEYE-------------------------------       129
tr|A0A2K9VME2|A0A2K9VME2_9CAUD      ------ANCDIEVTGD--KFPDPMKAEYEIDAITHYDSIDDRFYVFDLL-----------       149
tr|A0A249XWD5|A0A249XWD5_9CAUD      ------ANCDIEVTGD--KFPDPMKAEYEI------------------------------       130
sp|P04415|DPOL_BPT4                 ------ANCDIEVTGD--KFPDPMKAEYEI------------------------------       130
tr|A0A2U7NJH8|A0A2U7NJH8_9CAUD      ------CNVDIETTSPI-GFPDPK------------------------------------       123
tr|A0A0B5A2H2|A0A0B5A2H2_9CAUD      ------VNYDIEVTAP--EFPNAS------------------------------------       124
sp|Q38087|DPOL_BPR69                ------ANFDIEVTSPD-GFPEPS------------------------------------       127
tr|A0A1Z1LY62|A0A1Z1LY62_9CAUD      ------ANCDIEVTAP--EFPDPS------------------------------------       126
tr|A0A1S7DLM5|A0A1S7DLM5_MCV2       IEPNGCYRVPDAE--------------L--------EPVCARCFHCA----APRRAFATR       152
tr|Q6TUX3|Q6TUX3_YMTV5              VCPDGCYVIDIKM--------------L--------EKINDNCYHCN----DPQQLFLNP       152
sp|P0DOO5|DPOL_VAR67                ISPDGCYSLDDQY--------------L--------TKINNGCYHCG----DPRNCFAKE       152
sp|P0DOO6|DPOL_VARV                 ISPDGCYSLDDQY--------------L--------TKINNGCYHCG----DPRNCFAKE       152
sp|A0A7H0DN44|DPOL_MONPV            ISPDGCYSLDEQY--------------L--------TKINNGCYHCD----DPRNCFAKE       152
sp|O57191|DPOL_VACCA                ISPDGCYSLDEQY--------------L--------TKINNGCYHCD----DPRNCFAKK       152
tr|A0A287NEC0|A0A287NEC0_HORVV      --PAGKYSKAT------------RVMSY--------CQLELDCLYSDLVSHAPEGEYSK-       328
tr|A0A3B6JHK9|A0A3B6JHK9_WHEAT      --PAGKYRKAT------------RVMSY--------CQLELDCLYSDLVSHAPEGEYSK-       308
tr|A0A1D6QLT8|A0A1D6QLT8_MAIZE      --PAGKYRKAA------------CIMSY--------CQLELDCLYSDLVSHAAEGEYSK-       308
sp|Q9LRE6|DPOD1_ORYSJ               --PAGKYMKAA------------RIMSY--------CQLELDCLYSDLVSHAAEGEHSK-       310
sp|Q9LVN7|DPOD1_ARATH               --PTGKYKKNA------------RTLSY--------CQLEFHCLYSDLISHAAEGEYSK-       302
tr|A0A078I2E2|A0A078I2E2_BRANA      --PAGKYKKDA------------RTLSY--------CQLEFHCLYSDLISHAPEGEYSK-       297
tr|D0VEW7|D0VEW7_XENLA              --PAGKYRVRKESQDEEPSKDNPSKVSL--------AQIEVDISWADLISHPAEGEWQK-       310
tr|G3V8M1|G3V8M1_RAT                --PAGKYVRRAEK-----------KATL--------CQLEVDVLWSDVISHPPEGQWQR-       302
sp|P52431|DPOD1_MOUSE               --PAGKYVRRAEK-----------KATL--------CQLEVDVLWSDVISHPPEGQWQR-       304
sp|P28340|DPOD1_HUMAN               --PAGKYALRLKE-----------KATQ--------CQLEADVLWSDVVSHPPEGPWQR-       306
tr|F7DXU3|F7DXU3_HORSE              --PAGKYVLRPKG-----------KTTL--------CQLEADVLWSDVISHAPEGQWQR-       306
tr|M3VUJ4|M3VUJ4_FELCA              --PAGKYLLRLEG-----------KATH--------CQLEADVQWSDVVSHPPEGEWQR-       306
tr|A0A5G2QET9|A0A5G2QET9_PIG        --PAGKYLLRPEG-----------KATL--------CQLEADVLWSDVVSHPPEGPWQR-       306
tr|E1BNZ6|E1BNZ6_BOVIN              --PAGKYILRPEG-----------KATL--------CQLEADVLWSDVISHPPEGEWQR-       305
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tr|A8ALP2|A8ALP2_CITK8              -EGDTKDGAIVNARLKPHPDYRPPLKWVSLDIETTR------HGELYCIGLQGC--G---       174
tr|D2TGG5|D2TGG5_CITRI              -DGEARDGALVNARLKPHPDYRPPLRWLSLDIETTR------HGELYCIGLEGC--G---       174
tr|A0A5Y2S1M3|A0A5Y2S1M3_SALER      -DGEMRNGVIRNARLKPHPDYRPPLKWVSLDIETTR------HGELYCIGLEGC--G---       174
tr|A0A2B7LUW5|A0A2B7LUW5_9ESCH      -DGDFRDGAIVNARLKPNPDYRPPLKWVSIDIETTR------HGELYCIGLEGC--G---       174
tr|B7LVT1|B7LVT1_ESCF3              -EGDMHNGAIVNARLKPHPDYRPPLKWVSIDIETTR------HGELYCIGLEGC--G---       174
tr|A0A6N3R803|A0A6N3R803_SHIFL      -EGDMHNGTIVNARLKPHPDYRPPLKWVSIDIETTR------HGELYCIGLEGC--G---       174
sp|P21189|DPO2_ECOLI                -EGDMHNGTIVNARLKPHPDYRPPLKWVSIDIETTR------HGELYCIGLEGC--G---       174
tr|A0A3P6LPK6|A0A3P6LPK6_SHIDY      -EGDMHNGTIVNARLKPHPDYRPPLKWVSIDIETTR------HGELYCIGLEGC--G---       174
tr|A0A0K0QSA0|A0A0K0QSA0_9CAUD      --------------------------EAKYAIDAITH-YDSVEDKFFVYDLVE---GGLD       156
tr|A0A1W5P0A4|A0A1W5P0A4_9CAUD      --------------------------EAKYAIDAITH-YDSVEDKFFVYDLVE---GGLD       156
tr|A0A7U3VGB5|A0A7U3VGB5_9CAUD      --------------------------FAKYEIDAITH-YDSIEDKYFVFDLLNSARGRVT       158
tr|A0A5Q2F6H2|A0A5Q2F6H2_9CAUD      -------------------------------IDAITH-YDSVDDKFYVFDLLHSLYGSVS       157
tr|A0A2K9VME2|A0A2K9VME2_9CAUD      --NSMYGVRVANCDIEVTGDKFPDPMKAEYEIDAITH-YDSIDDRFYVFDLLNSMYGSVS       206
tr|A0A249XWD5|A0A249XWD5_9CAUD      --------------------------------DAITH-YDSIDDRFYVFDLLNSMYGSVS       157
sp|P04415|DPOL_BPT4                 --------------------------------DAITH-YDSIDDRFYVFDLLNSMYGSVS       157
tr|A0A2U7NJH8|A0A2U7NJH8_9CAUD      --------------------------AALHPIDAITH-YDSIDDKFYVFDLLHSPYGNVT       156
tr|A0A0B5A2H2|A0A0B5A2H2_9CAUD      --------------------------QALYPVDALTH-YDSVANKFYVFDLLNSPYGSVT       157
sp|Q38087|DPOL_BPR69                --------------------------QAKHPIDAITH-YDSIDDRFYVFDLLNSPYGNVE       160
tr|A0A1Z1LY62|A0A1Z1LY62_9CAUD      --------------------------QALYPIDAITH-YDSIDDRFYVFDLLNSPYGSVT       159
tr|A0A1S7DLM5|A0A1S7DLM5_MCV2       VPLFEVTHTYLFFDIECQFDK-KFPSVFSNPVSHISFCYVDRLGTEVRFSLINS--DLLP       209
tr|Q6TUX3|Q6TUX3_YMTV5              IPKFDVSRSYLFLDIECHFEK-KFPSVFTNPVSHVSCCYVNLFGRELKFTLINR--DMLS       209
sp|P0DOO5|DPOL_VAR67                IPRFDIPRSYLFLDIECHFDK-KFPSVFINPISHTSYCYIDLSGKRLLFTLINE--EMLT       209
sp|P0DOO6|DPOL_VARV                 IPRFDIPRSYLFLDIECHFDK-KFPSVFINPISHTSYCYIDLSGKRLLFTLINE--EMLT       209
sp|A0A7H0DN44|DPOL_MONPV            IPRFDIPRSYLFLDIECHFDK-KFPSVFINPISHTSYCYIDLSGKRLLFTLINE--EMLT       209
sp|O57191|DPOL_VACCA                IPRFDIPRSYLFLDIECHFDK-KFPSVFINPISHTSYCYIDLSGKRLLFTLINE--EMLT       209
tr|A0A287NEC0|A0A287NEC0_HORVV      ----MAPFRILSFDIECAGRKGHFPEPTHDPVIQIAN-LLTLQGEAQPFV----------       373
tr|A0A3B6JHK9|A0A3B6JHK9_WHEAT      ----MAPFRILSFDIECAGRKGHFPEPTHDPVIQIAN-LLTLQGEAQPFV----------       353
tr|A0A1D6QLT8|A0A1D6QLT8_MAIZE      ----MAPFRILSFDIECAGRKGHFPEPTHDPVIQIAN-LVTHQGEDQPFV----------       353
sp|Q9LRE6|DPOD1_ORYSJ               ----MAPFRILSFDIECAGRKGHFPEPTHDPVIQIAN-LVTLQGEGQPFV----------       355
sp|Q9LVN7|DPOD1_ARATH               ----MAPFRVLSFDIECAGRKGHFPEAKHDPVIQIAN-LVTLQGEDHPFV----------       347
tr|A0A078I2E2|A0A078I2E2_BRANA      ----MAPFRVLSFDIECAGRKGHFPEAKHDPVIQIAN-LVTLQGEDQPFI----------       342
tr|D0VEW7|D0VEW7_XENLA              ----IAPQRVLSFDIECAGRKGVFPEPDKDPVIQIAN-MVLRQGEKDPFI----------       355
tr|G3V8M1|G3V8M1_RAT                ----IAPLRVLSFDIECAGRKGIFPEPERDPVIQICS-LGLRWGEPEPFL----------       347
sp|P52431|DPOD1_MOUSE               ----IAPLRVLSFDIECAGRKGIFPEPERDPVIQICS-LGLRWGEPEPFL----------       349
sp|P28340|DPOD1_HUMAN               ----IAPLRVLSFDIECAGRKGIFPEPERDPVIQICS-LGLRWGEPEPFL----------       351
tr|F7DXU3|F7DXU3_HORSE              ----IAPLRVLSFDIECAGRKGIFPEPERDPVIQICS-LGLRWGEPEPFL----------       351
tr|M3VUJ4|M3VUJ4_FELCA              ----IAPLRVLSFDIECAGRKGIFPEPERDPVIQICS-LGLRWGEPEPFL----------       351
tr|A0A5G2QET9|A0A5G2QET9_PIG        ----IAPLRVLSFDIECAGRKGIFPEPERDPVIQICS-LGLRWGEPEPFL----------       351
tr|E1BNZ6|E1BNZ6_BOVIN              ----IAPLRVLSFDIECAGRKGIFPEPERDPVIQICS-LGLRWGEPEPFL----------       350
                                                                               .
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tr|A8ALP2|A8ALP2_CITK8              GWNVVQFDLRVLQKHAERYR---IPL---RLGRDNTELEWREHGFKNG----VF------       265
tr|D2TGG5|D2TGG5_CITRI              GWNLVQFDLRMLQKHAERYR---IPL---RFGRDSSELEWREHGFKNG----VY------       265
tr|A0A5Y2S1M3|A0A5Y2S1M3_SALER      GWNVVQFDLRMLQKHAERYR---IPL---RLGRDNSELEWREHGFKNG----VF------       265
tr|A0A2B7LUW5|A0A2B7LUW5_9ESCH      GWNVVQFDLRMLQKHAERYR---IPL---RLGRDNSELEWREHGFKNG----VF------       265
tr|B7LVT1|B7LVT1_ESCF3              GWNVVQFDLRMLQKHAERYR---IPL---RLGRDNSELEWREHGFKNG----VF------       265
tr|A0A6N3R803|A0A6N3R803_SHIFL      GWNVVQFDLRMLQKHAERYR---LPL---RLGRDNSELEWREHGFKNG----VF------       265
sp|P21189|DPO2_ECOLI                GWNVVQFDLRMLQKHAERYR---LPL---RLGRDNSELEWREHGFKNG----VF------       265
tr|A0A3P6LPK6|A0A3P6LPK6_SHIDY      GWNVVQFDLRMLQKHAERYR---LPL---RLGRDNSELEWREHGFKNG----VF------       265
tr|A0A0K0QSA0|A0A0K0QSA0_9CAUD      GWNSNKFDIAYIITRYLNIFGQNVVRHFSPFGKVTAKTTTDQYG--NE----QL------       253
tr|A0A1W5P0A4|A0A1W5P0A4_9CAUD      GWNSNKFDIAYIITRYLNIFGQNVVRHFSPFGKVTAKTTTDHYG--NE----QL------       253
tr|A0A7U3VGB5|A0A7U3VGB5_9CAUD      GWNVEGFDIPYIVNRIKNVLGVSGMSRLSPFGKITSKVITNMYG--DK----EI------       260
tr|A0A5Q2F6H2|A0A5Q2F6H2_9CAUD      GWNIEGFDIPYIMNRVKQILGERTMKRFSPLNKVSSKIITNMYG--DK----EI------       259
tr|A0A2K9VME2|A0A2K9VME2_9CAUD      GWNIEGFDVPYIMNRVKMILGERSMKRFSPIGRVKSKLIQNMYG--SK----EI------       308
tr|A0A249XWD5|A0A249XWD5_9CAUD      GWNIEGFDVPYIMNRVKMVLGERSMKRFSPIGRVKSKLIQNVYG--SK----EI------       259
sp|P04415|DPOL_BPT4                 GWNIEGFDVPYIMNRVKMILGERSMKRFSPIGRVKSKLIQNMYG--SK----EI------       259
tr|A0A2U7NJH8|A0A2U7NJH8_9CAUD      GWNIEGFDIPYIYQRIENVLGRSTALRMSPIGSVRTKLVTTQYG--EE----RL------       258
tr|A0A0B5A2H2|A0A0B5A2H2_9CAUD      GWNVEGFDNPYMYNRLKNVFGENTAKRLSPNRKVNSKIIQNIYG--DK----EV------       259
sp|Q38087|DPOL_BPR69                GWNVESFDIPYVYNRIKNIFGESTAKRLSPHRKTRVKVIENMYG--SR----EI------       262
tr|A0A1Z1LY62|A0A1Z1LY62_9CAUD      GWNTESFDIPYIYNRIKNVFGEKTANRLSPHRRTKSKIIQNMYG--ER----EV------       261
tr|A0A1S7DLM5|A0A1S7DLM5_MCV2       TFNGNNFDIRYVSNRLQLLTQSSVCFR-LPDQREPVKLVIYERSLASHRGAGGMANTSFH       314
tr|Q6TUX3|Q6TUX3_YMTV5              TFNGHNFDLRYISNRLELLTSGKIYFR-SPDKKETVHMCIYERNLSSHKGACGVSNTTYH       319
sp|P0DOO5|DPOL_VAR67                TFNGHNFDLRYITNRLELLTGEKIIFR-SPDKKEAVHLCIYERNQSSHKGVGGMANTTFH       319
sp|P0DOO6|DPOL_VARV                 TFNGHNFDLRYITNRLELLTGEKIIFR-SPDKKEAVHLCIYERNQSSHKGVGGMANTTFH       319
sp|A0A7H0DN44|DPOL_MONPV            TFNGHNFDLRYITNRLELLTGEKIIFR-SPDKKEAVHLCIYERNQSSHKGVCGMANTTFH       319
sp|O57191|DPOL_VACCA                TFNGHNFDLRYITNRLELLTGEKIIFR-SPDKKEAVHLCIYERNQSSHKGVGGMANTTFH       319
tr|A0A287NEC0|A0A287NEC0_HORVV      GYNICKFDLPYLIEVHQVLKIVEFPLL-GRIR--NSRVRVRDTTFNSR----QYGMRESK       469
tr|A0A3B6JHK9|A0A3B6JHK9_WHEAT      GYNICKFDLPYLIERAEVLKIVEFPLL-GRIR--NSRVRVRDTTFNSR----QYGMRESK       449
tr|A0A1D6QLT8|A0A1D6QLT8_MAIZE      GYNICKFDMPYLIERAEVLKIAEFPIL-GRIR--NSRVRVRDTTFSSR----QYGVRESK       449
sp|Q9LRE6|DPOD1_ORYSJ               GYNICKFDLPYLIERAEVLKIVEFPIL-GRIR--NSRVRVRDTTFSSR----QYGMRESK       451
sp|Q9LVN7|DPOD1_ARATH               GYNICKFDLPYLIERAATLGIEEFPLL-GRVK--NSRVRVRDSTFSSR----QQGIRESK       443
tr|A0A078I2E2|A0A078I2E2_BRANA      GYNICKFDLPYLIERAAALGIEEFPLL-GRVK--NSRVRMRDSTFSSR----QQGTRESK       438
tr|D0VEW7|D0VEW7_XENLA              GYNIQNFDMPYLINRAQTLKVSTFPFL-GRIR--SLKSVIRDSSFQSK----QMGRRENK       451
tr|G3V8M1|G3V8M1_RAT                GYNIQNFDLPYLISRAQTLKVDRFPFL-GRVT--GLRSNIRDSSFQSR----QVGRRDSK       443
sp|P52431|DPOD1_MOUSE               GYNIQNFDLPYLISRAQALKVDRFPFL-GRVT--GLRSNIRDSSFQSR----QVGRRDSK       445
sp|P28340|DPOD1_HUMAN               GYNIQNFDLPYLISRAQTLKVQTFPFL-GRVA--GLCSNIRDSSFQSK----QTGRRDTK       447
tr|F7DXU3|F7DXU3_HORSE              GYNIQNFDLPYLISRAQTLKVSSFPFL-GRVS--GLRSNIRDSSFQSK----QTGRRDTK       447
tr|M3VUJ4|M3VUJ4_FELCA              GYNIQNFDLPYLISRAQTLKVESFPFL-GRVS--GLRSTIRDSSFQSK----QTGRRDSK       447
tr|A0A5G2QET9|A0A5G2QET9_PIG        GYNIQNFDLPYLISRAQTLKVQTFPFL-GRVS--GLRSNIRDSSFQSK----QTGRRDSK       447
tr|E1BNZ6|E1BNZ6_BOVIN              GYNIQNFDLPYLISRAQTLKVPGFPLL-GRVI--GLRSNIRESSFQSR----QTGRRDSK       446
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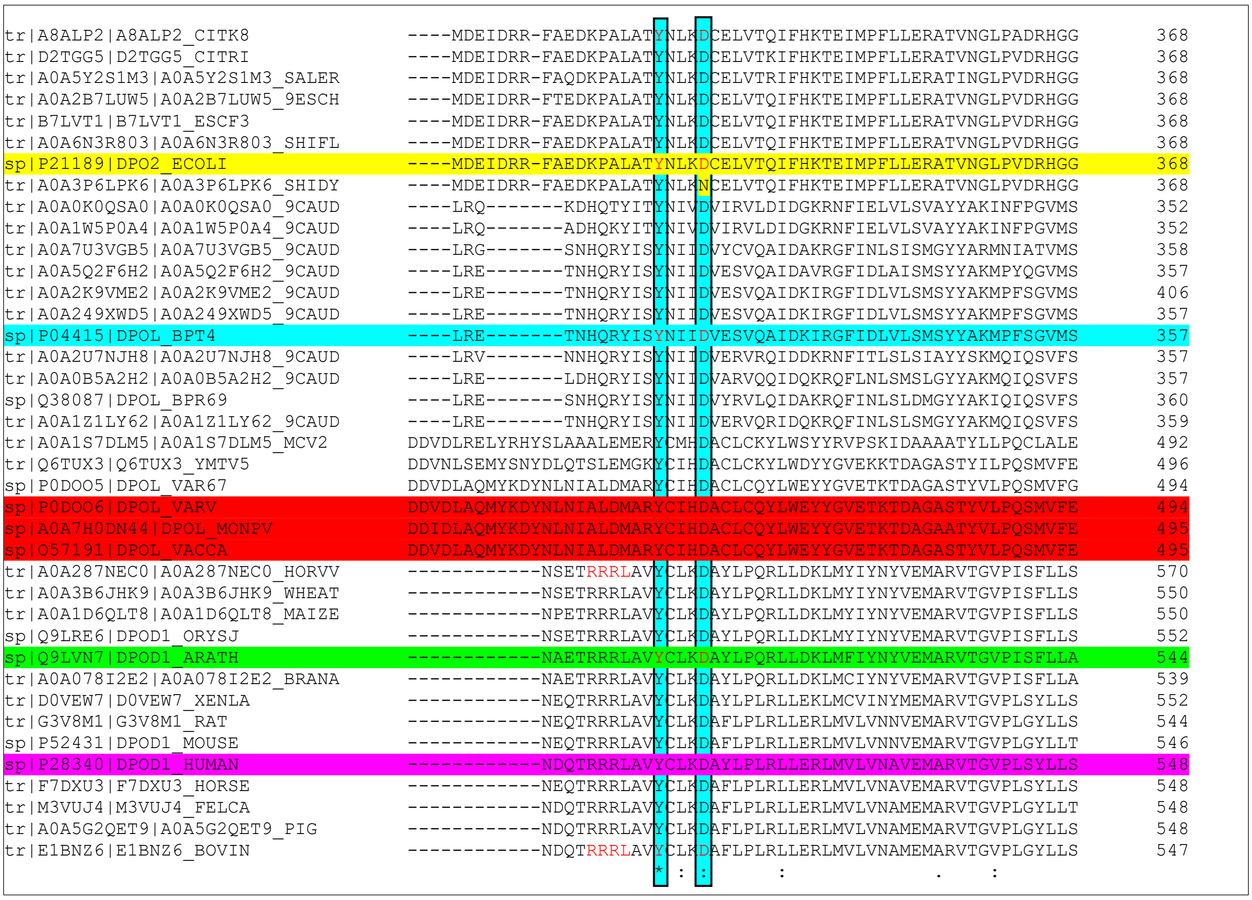

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tr|D2TGG5|D2TGG5_CITRI              ----MDEIDRR-FAEDKPALATYNLKDCELVTKIFHKTEIMPFLLERATVNGLPVDRHGG       368
tr|A0A5Y2S1M3|A0A5Y2S1M3_SALER      ----MDEIDRR-FAQDKPALATYNLKDCELVTRIFHKTEIMPFLLERATINGLPVDRHGG       368
tr|A0A2B7LUW5|A0A2B7LUW5_9ESCH      ----MDEIDRR-FTEDKPALATYNLKDCELVTQIFHKTEIMPFLLERATVNGLPVDRHGG       368
tr|B7LVT1|B7LVT1_ESCF3              ----MDEIDRR-FAEDKPALATYNLKDCELVTQIFHKTEIMPFLLERATVNGLPVDRHGG       368
tr|A0A6N3R803|A0A6N3R803_SHIFL      ----MDEIDRR-FAEDKPALATYNLKDCELVTQIFHKTEIMPFLLERATVNGLPVDRHGG       368
sp|P21189|DPO2_ECOLI                ----MDEIDRR-FAEDKPALATYNLKDCELVTQIFHKTEIMPFLLERATVNGLPVDRHGG       368
tr|A0A3P6LPK6|A0A3P6LPK6_SHIDY      ----MDEIDRR-FAEDKPALATYNLKNCELVTQIFHKTEIMPFLLERATVNGLPVDRHGG       368
tr|A0A0K0QSA0|A0A0K0QSA0_9CAUD      ----LRQ-------KDHQTYITYNIVDVIRVLDIDGKRNFIELVLSVAYYAKINFPGVMS       352
tr|A0A1W5P0A4|A0A1W5P0A4_9CAUD      ----LRQ-------ADHQKYITYNIVDVIRVLDIDGKRNFIELVLSVAYYAKINFPGVMS       352
tr|A0A7U3VGB5|A0A7U3VGB5_9CAUD      ----LRG-------SNHQRYISYNIIDVYCVQAIDAKRGFINLSISMGYYARMNIATVMS       358
tr|A0A5Q2F6H2|A0A5Q2F6H2_9CAUD      ----LRE-------TNHQRYISYNIIDVESVQAIDAVRGFIDLAISMSYYAKMPYQGVMS       357
tr|A0A2K9VME2|A0A2K9VME2_9CAUD      ----LRE-------TNHQRYISYNIIDVESVQAIDKIRGFIDLVLSMSYYAKMPFSGVMS       406
tr|A0A249XWD5|A0A249XWD5_9CAUD      ----LRE-------TNHQRYISYNIIDVESVQAIDKIRGFIDLVLSMSYYAKMPFSGVMS       357
sp|P04415|DPOL_BPT4                 ----LRE-------TNHQRYISYNIIDVESVQAIDKIRGFIDLVLSMSYYAKMPFSGVMS       357
tr|A0A2U7NJH8|A0A2U7NJH8_9CAUD      ----LRV-------NNHQRYISYNIIDVERVRQIDDKRNFITLSLSIAYYSKMQIQSVFS       357
tr|A0A0B5A2H2|A0A0B5A2H2_9CAUD      ----LRE-------LDHQRYISYNIIDVARVQQIDQKRQFLNLSMSLGYYAKMQIQSVFS       357
sp|Q38087|DPOL_BPR69                ----LRE-------SNHQRYISYNIIDVYRVLQIDAKRQFINLSLDMGYYAKIQIQSVFS       360
tr|A0A1Z1LY62|A0A1Z1LY62_9CAUD      ----LRE-------TNHQRYISYNIIDVERVQRIDQKRQFINLSLSMGYYAKMQIQSVFS       359
tr|A0A1S7DLM5|A0A1S7DLM5_MCV2       DDVDLRELYRHYSLAAALEMERYCMHDACLCKYLWSYYRVPSKIDAAAATYLLPQCLALE       492
tr|Q6TUX3|Q6TUX3_YMTV5              DDVNLSEMYSNYDLQTSLEMGKYCIHDACLCKYLWDYYGVEKKTDAGASTYILPQSMVFE       496
sp|P0DOO5|DPOL_VAR67                DDVDLAQMYKDYNLNIALDMARYCIHDACLCQYLWEYYGVETKTDAGASTYVLPQSMVFG       494
sp|P0DOO6|DPOL_VARV                 DDVDLAQMYKDYNLNIALDMARYCIHDACLCQYLWEYYGVETKTDAGASTYVLPQSMVFE       494
sp|A0A7H0DN44|DPOL_MONPV            DDIDLAQMYKDYNLNIALDMARYCIHDACLCQYLWEYYGVETKTDAGAATYVLPQSMVFE       495
sp|O57191|DPOL_VACCA                DDVDLAQMYKDYNLNIALDMARYCIHDACLCQYLWEYYGVETKTDAGASTYVLPQSMVFE       495
tr|A0A287NEC0|A0A287NEC0_HORVV      ------------NSETRRRLAVYCLKDAYLPQRLLDKLMYIYNYVEMARVTGVPISFLLS       570
tr|A0A3B6JHK9|A0A3B6JHK9_WHEAT      ------------NSETRRRLAVYCLKDAYLPQRLLDKLMYIYNYVEMARVTGVPISFLLS       550
tr|A0A1D6QLT8|A0A1D6QLT8_MAIZE      ------------NPETRRRLAVYCLKDAYLPQRLLDKLMYIYNYVEMARVTGVPISFLLS       550
sp|Q9LRE6|DPOD1_ORYSJ               ------------NSETRRRLAVYCLKDAYLPQRLLDKLMYIYNYVEMARVTGVPISFLLS       552
sp|Q9LVN7|DPOD1_ARATH               ------------NAETRRRLAVYCLKDAYLPQRLLDKLMFIYNYVEMARVTGVPISFLLA       544
tr|A0A078I2E2|A0A078I2E2_BRANA      ------------NAETRRRLAVYCLKDAYLPQRLLDKLMCIYNYVEMARVTGVPISFLLA       539
tr|D0VEW7|D0VEW7_XENLA              ------------NEQTRRRLAVYCLKDAYLPLRLLEKLMCVINYMEMARVTGVPLSYLLS       552
tr|G3V8M1|G3V8M1_RAT                ------------NEQTRRRLAVYCLKDAFLPLRLLERLMVLVNNVEMARVTGVPLGYLLS       544
sp|P52431|DPOD1_MOUSE               ------------NEQTRRRLAVYCLKDAFLPLRLLERLMVLVNNVEMARVTGVPLGYLLT       546
sp|P28340|DPOD1_HUMAN               ------------NDQTRRRLAVYCLKDAYLPLRLLERLMVLVNAVEMARVTGVPLSYLLS       548
tr|F7DXU3|F7DXU3_HORSE              ------------NEQTRRRLAVYCLKDAFLPLRLLERLMVLVNAVEMARVTGVPLSYLLS       548
tr|M3VUJ4|M3VUJ4_FELCA              ------------NDQTRRRLAVYCLKDAFLPLRLLERLMVLVNAMEMARVTGVPLGYLLT       548
tr|A0A5G2QET9|A0A5G2QET9_PIG        ------------NDQTRRRLAVYCLKDAFLPLRLLERLMVLVNAMEMARVTGVPLGYLLS       548
tr|E1BNZ6|E1BNZ6_BOVIN              ------------NDQTRRRLAVYCLKDAFLPLRLLERLMVLVNAMEMARVTGVPLGYLLS       547
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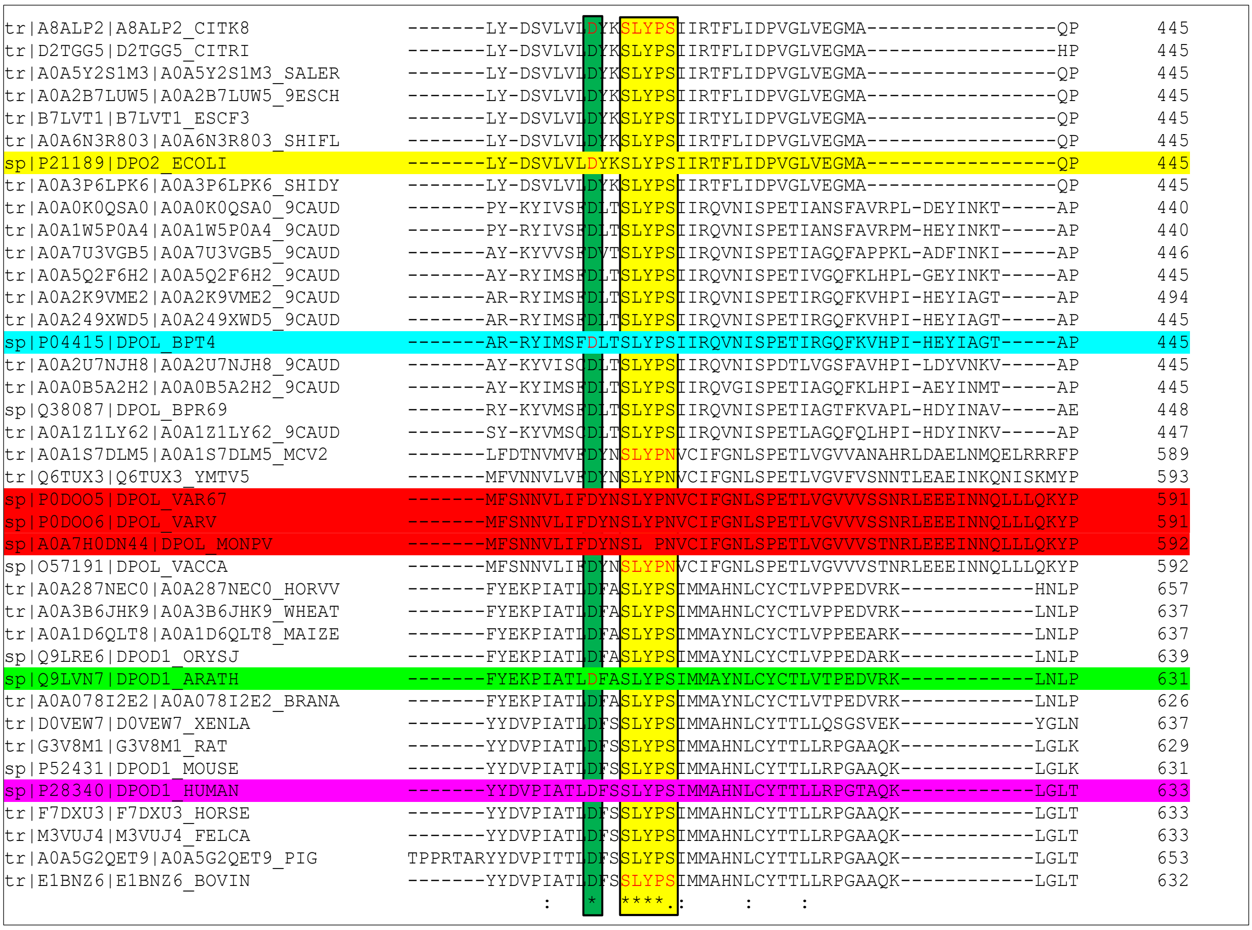

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tr|A8ALP2|A8ALP2_CITK8              -------LY-DSVLVLDYKSLYPSIIRTFLIDPVGLVEGMA-----------------QP       445
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tr|A0A5Y2S1M3|A0A5Y2S1M3_SALER      -------LY-DSVLVLDYKSLYPSIIRTFLIDPVGLVEGMA-----------------QP       445
tr|A0A2B7LUW5|A0A2B7LUW5_9ESCH      -------LY-DSVLVLDYKSLYPSIIRTFLIDPVGLVEGMA-----------------QP       445
tr|B7LVT1|B7LVT1_ESCF3              -------LY-DSVLVLDYKSLYPSIIRTYLIDPVGLVEGMA-----------------QP       445
tr|A0A6N3R803|A0A6N3R803_SHIFL      -------LY-DSVLVLDYKSLYPSIIRTFLIDPVGLVEGMA-----------------QP       445
sp|P21189|DPO2_ECOLI                -------LY-DSVLVLDYKSLYPSIIRTFLIDPVGLVEGMA-----------------QP       445
tr|A0A3P6LPK6|A0A3P6LPK6_SHIDY      -------LY-DSVLVLDYKSLYPSIIRTFLIDPVGLVEGMA-----------------QP       445
tr|A0A0K0QSA0|A0A0K0QSA0_9CAUD      -------PY-KYIVSFDLTSLYPSIIRQVNISPETIANSFAVRPL-DEYINKT-----AP       440
tr|A0A1W5P0A4|A0A1W5P0A4_9CAUD      -------PY-RYIVSFDLTSLYPSIIRQVNISPETIANSFAVRPM-HEYINKT-----AP       440
tr|A0A7U3VGB5|A0A7U3VGB5_9CAUD      -------AY-KYVVSFDVTSLYPSIIRQVNISPETIAGQFAPPKL-ADFINKI-----AP       446
tr|A0A5Q2F6H2|A0A5Q2F6H2_9CAUD      -------AY-RYIMSFDLTSLYPSIIRQVNISPETIVGQFKLHPL-GEYINKT-----AP       445
tr|A0A2K9VME2|A0A2K9VME2_9CAUD      -------AR-RYIMSFDLTSLYPSIIRQVNISPETIRGQFKVHPI-HEYIAGT-----AP       494
tr|A0A249XWD5|A0A249XWD5_9CAUD      -------AR-RYIMSFDLTSLYPSIIRQVNISPETIRGQFKVHPI-HEYIAGT-----AP       445
sp|P04415|DPOL_BPT4                 -------AR-RYIMSFDLTSLYPSIIRQVNISPETIRGQFKVHPI-HEYIAGT-----AP       445
tr|A0A2U7NJH8|A0A2U7NJH8_9CAUD      -------AY-KYVISCDLTSLYPSIIRQVNISPDTLVGSFAVHPI-LDYVNKV-----AP       445
tr|A0A0B5A2H2|A0A0B5A2H2_9CAUD      -------AY-KYIMSFDLTSLYPSIIRQVGISPETIAGQFKLHPI-AEYINMT-----AP       445
sp|Q38087|DPOL_BPR69                -------RY-KYVMSFDLTSLYPSIIRQVNISPETIAGTFKVAPL-HDYINAV-----AE       448
tr|A0A1Z1LY62|A0A1Z1LY62_9CAUD      -------SY-KYVMSCDLTSLYPSIIRQVNISPETLAGQFQLHPI-HDYINKV-----AP       447
tr|A0A1S7DLM5|A0A1S7DLM5_MCV2       -------LFDTNVMVFDYNSLYPNVCIFGNLSPETLVGVVANAHRLDAELNMQELRRRFP       589
tr|Q6TUX3|Q6TUX3_YMTV5              -------MFVNNVLVFDYNSLYPNVCIFGNLSPETLVGVFVSNNTLEAEINKQNISKMYP       593
sp|P0DOO5|DPOL_VAR67                -------MFSNNVLIFDYNSLYPNVCIFGNLSPETLVGVVVSSNRLEEEINNQLLLQKYP       591
sp|P0DOO6|DPOL_VARV                 -------MFSNNVLIFDYNSLYPNVCIFGNLSPETLVGVVVSSNRLEEEINNQLLLQKYP       591
sp|A0A7H0DN44|DPOL_MONPV            -------MFSNNVLIFDYNSL PNVCIFGNLSPETLVGVVVSTNRLEEEINNQLLLQKYP       592
sp|O57191|DPOL_VACCA                -------MFSNNVLIFDYNSLYPNVCIFGNLSPETLVGVVVSTNRLEEEINNQLLLQKYP       592
tr|A0A287NEC0|A0A287NEC0_HORVV      -------FYEKPIATLDFASLYPSIMMAHNLCYCTLVPPEDVRK------------HNLP       657
tr|A0A3B6JHK9|A0A3B6JHK9_WHEAT      -------FYEKPIATLDFASLYPSIMMAHNLCYCTLVPPEDVRK------------LNLP       637
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sp|Q9LRE6|DPOD1_ORYSJ               -------FYEKPIATLDFASLYPSIMMAYNLCYCTLVPPEDARK------------LNLP       639
sp|Q9LVN7|DPOD1_ARATH               -------FYEKPIATLDFASLYPSIMMAYNLCYCTLVTPEDVRK------------LNLP       631
tr|A0A078I2E2|A0A078I2E2_BRANA      -------FYEKPIATLDFASLYPSIMMAYNLCYCTLVTPEDVRK------------LNLP       626
tr|D0VEW7|D0VEW7_XENLA              -------YYDVPIATLDFSSLYPSIMMAHNLCYTTLLQSGSVEK------------YGLN       637
tr|G3V8M1|G3V8M1_RAT                -------YYDVPIATLDFSSLYPSIMMAHNLCYTTLLRPGAAQK------------LGLK       629
sp|P52431|DPOD1_MOUSE               -------YYDVPIATLDFSSLYPSIMMAHNLCYTTLLRPGAAQK------------LGLK       631
sp|P28340|DPOD1_HUMAN               -------YYDVPIATLDFSSLYPSIMMAHNLCYTTLLRPGTAQK------------LGLT       633
tr|F7DXU3|F7DXU3_HORSE              -------YYDVPIATLDFSSLYPSIMMAHNLCYTTLLRPGAAQK------------LGLT       633
tr|M3VUJ4|M3VUJ4_FELCA              -------YYDVPIATLDFSSLYPSIMMAHNLCYTTLLRPGAAQK------------LGLT       633
tr|A0A5G2QET9|A0A5G2QET9_PIG        TPPRTARYYDVPITTLDFSSLYPSIMMAHNLCYTTLLRPGAAQK------------LGLT       653
tr|E1BNZ6|E1BNZ6_BOVIN              -------YYDVPIATLDFSSLYPSIMMAHNLCYTTLLRPGAAQK------------LGLT       632
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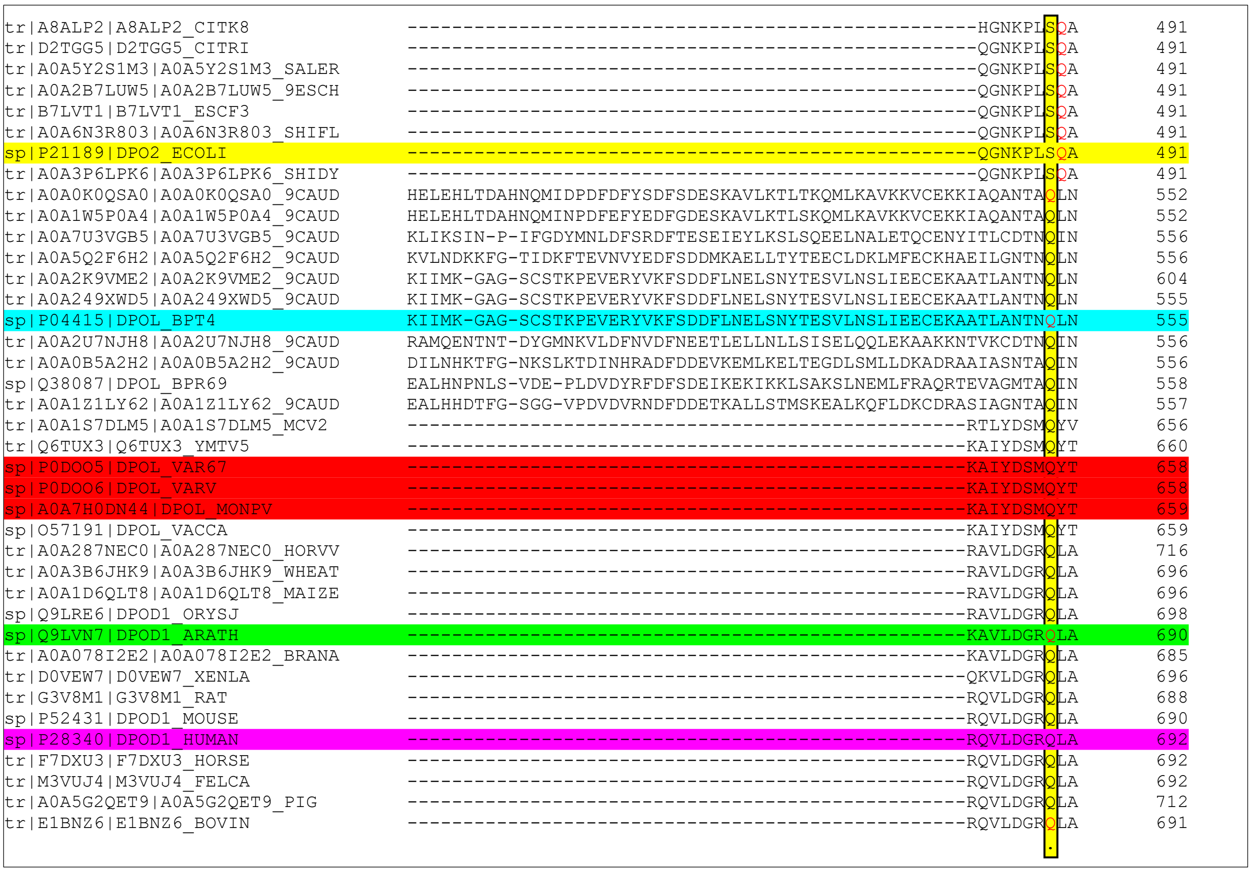

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tr|A0A2B7LUW5|A0A2B7LUW5_9ESCH      ---------------------------------------------------QGNKPLSQA       491
tr|B7LVT1|B7LVT1_ESCF3              ---------------------------------------------------QGNKPLSQA       491
tr|A0A6N3R803|A0A6N3R803_SHIFL      ---------------------------------------------------QGNKPLSQA       491
sp|P21189|DPO2_ECOLI                ---------------------------------------------------QGNKPLSQA       491
tr|A0A3P6LPK6|A0A3P6LPK6_SHIDY      ---------------------------------------------------QGNKPLSQA       491
tr|A0A0K0QSA0|A0A0K0QSA0_9CAUD      HELEHLTDAHNQMIDPDFDFYSDFSDESKAVLKTLTKQMLKAVKKVCEKKIAQANTAQLN       552
tr|A0A1W5P0A4|A0A1W5P0A4_9CAUD      HELEHLTDAHNQMINPDFEFYEDFGDESKAVLKTLSKQMLKAVKKVCEKKIAQANTAQLN       552
tr|A0A7U3VGB5|A0A7U3VGB5_9CAUD      KLIKSIN-P-IFGDYMNLDFSRDFTESEIEYLKSLSQEELNALETQCENYITLCDTNQIN       556
tr|A0A5Q2F6H2|A0A5Q2F6H2_9CAUD      KVLNDKKFG-TIDKFTEVNVYEDFSDDMKAELLTYTEECLDKLMFECKHAEILGNTNQLN       556
tr|A0A2K9VME2|A0A2K9VME2_9CAUD      KIIMK-GAG-SCSTKPEVERYVKFSDDFLNELSNYTESVLNSLIEECEKAATLANTNQLN       604
tr|A0A249XWD5|A0A249XWD5_9CAUD      KIIMK-GAG-SCSTKPEVERYVKFSDDFLNELSNYTESVLNSLIEECEKAATLANTNQLN       555
sp|P04415|DPOL_BPT4                 KIIMK-GAG-SCSTKPEVERYVKFSDDFLNELSNYTESVLNSLIEECEKAATLANTNQLN       555
tr|A0A2U7NJH8|A0A2U7NJH8_9CAUD      RAMQENTNT-DYGMNKVLDFNVDFNEETLELLNLLSISELQQLEKAAKKNTVKCDTNQIN       556
tr|A0A0B5A2H2|A0A0B5A2H2_9CAUD      DILNHKTFG-NKSLKTDINHRADFDDEVKEMLKELTEGDLSMLLDKADRAAIASNTAQIN       556
sp|Q38087|DPOL_BPR69                EALHNPNLS-VDE-PLDVDYRFDFSDEIKEKIKKLSAKSLNEMLFRAQRTEVAGMTAQIN       558
tr|A0A1Z1LY62|A0A1Z1LY62_9CAUD      EALHHDTFG-SGG-VPDVDVRNDFDDETKALLSTMSKEALKQFLDKCDRASIAGNTAQIN       557
tr|A0A1S7DLM5|A0A1S7DLM5_MCV2       --------------------------------------------------RTLYDSMQYV       656
tr|Q6TUX3|Q6TUX3_YMTV5              --------------------------------------------------KAIYDSMQYT       660
sp|P0DOO5|DPOL_VAR67                --------------------------------------------------KAIYDSMQYT       658
sp|P0DOO6|DPOL_VARV                 --------------------------------------------------KAIYDSMQYT       658
sp|A0A7H0DN44|DPOL_MONPV            --------------------------------------------------KAIYDSMQYT       659
sp|O57191|DPOL_VACCA                --------------------------------------------------KAIYDSMQYT       659
tr|A0A287NEC0|A0A287NEC0_HORVV      --------------------------------------------------RAVLDGRQLA       716
tr|A0A3B6JHK9|A0A3B6JHK9_WHEAT      --------------------------------------------------RAVLDGRQLA       696
tr|A0A1D6QLT8|A0A1D6QLT8_MAIZE      --------------------------------------------------RAVLDGRQLA       696
sp|Q9LRE6|DPOD1_ORYSJ               --------------------------------------------------RAVLDGRQLA       698
sp|Q9LVN7|DPOD1_ARATH               --------------------------------------------------KAVLDGRQLA       690
tr|A0A078I2E2|A0A078I2E2_BRANA      --------------------------------------------------KAVLDGRQLA       685
tr|D0VEW7|D0VEW7_XENLA              --------------------------------------------------QKVLDGRQLA       696
tr|G3V8M1|G3V8M1_RAT                --------------------------------------------------RQVLDGRQLA       688
sp|P52431|DPOD1_MOUSE               --------------------------------------------------RQVLDGRQLA       690
sp|P28340|DPOD1_HUMAN               --------------------------------------------------RQVLDGRQLA       692
tr|F7DXU3|F7DXU3_HORSE              --------------------------------------------------RQVLDGRQLA       692
tr|M3VUJ4|M3VUJ4_FELCA              --------------------------------------------------RQVLDGRQLA       692
tr|A0A5G2QET9|A0A5G2QET9_PIG        --------------------------------------------------RQVLDGRQLA       712
tr|E1BNZ6|E1BNZ6_BOVIN              --------------------------------------------------RQVLDGRQLA       691
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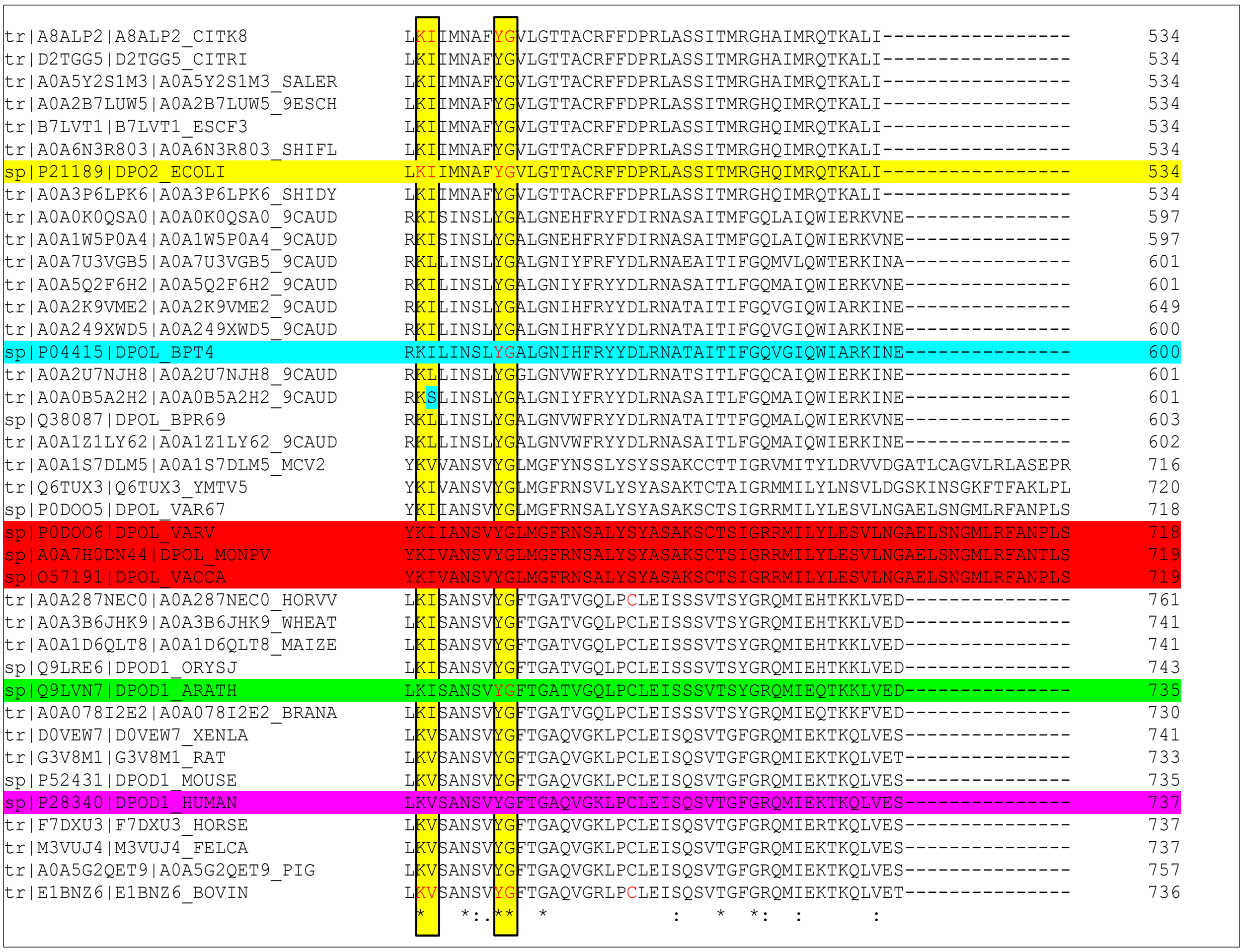

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tr|D2TGG5|D2TGG5_CITRI              LKIIMNAFYGVLGTTACRFFDPRLASSITMRGHAIMRQTKALI-----------------       534
tr|A0A5Y2S1M3|A0A5Y2S1M3_SALER      LKIIMNAFYGVLGTTACRFFDPRLASSITMRGHAIMRQTKALI-----------------       534
tr|A0A2B7LUW5|A0A2B7LUW5_9ESCH      LKIIMNAFYGVLGTTACRFFDPRLASSITMRGHQIMRQTKALI-----------------       534
tr|B7LVT1|B7LVT1_ESCF3              LKIIMNAFYGVLGTTACRFFDPRLASSITMRGHQIMRQTKALI-----------------       534
tr|A0A6N3R803|A0A6N3R803_SHIFL      LKIIMNAFYGVLGTTACRFFDPRLASSITMRGHQIMRQTKALI-----------------       534
sp|P21189|DPO2_ECOLI                LKIIMNAFYGVLGTTACRFFDPRLASSITMRGHQIMRQTKALI-----------------       534
tr|A0A3P6LPK6|A0A3P6LPK6_SHIDY      LKIIMNAFYGVLGTTACRFFDPRLASSITMRGHQIMRQTKALI-----------------       534
tr|A0A0K0QSA0|A0A0K0QSA0_9CAUD      RKISINSLYGALGNEHFRYFDIRNASAITMFGQLAIQWIERKVNE---------------       597
tr|A0A1W5P0A4|A0A1W5P0A4_9CAUD      RKISINSLYGALGNEHFRYFDIRNASAITMFGQLAIQWIERKVNE---------------       597
tr|A0A7U3VGB5|A0A7U3VGB5_9CAUD      RKLLINSLYGALGNIYFRFYDLRNAEAITIFGQMVLQWTERKINA---------------       601
tr|A0A5Q2F6H2|A0A5Q2F6H2_9CAUD      RKILINSLYGALGNIYFRYYDLRNASAITLFGQMAIQWIERKVNE---------------       601
tr|A0A2K9VME2|A0A2K9VME2_9CAUD      RKILINSLYGALGNIHFRYYDLRNATAITIFGQVGIQWIARKINE---------------       649
tr|A0A249XWD5|A0A249XWD5_9CAUD      RKILINSLYGALGNIHFRYYDLRNATAITIFGQVGIQWIARKINE---------------       600
sp|P04415|DPOL_BPT4                 RKILINSLYGALGNIHFRYYDLRNATAITIFGQVGIQWIARKINE---------------       600
tr|A0A2U7NJH8|A0A2U7NJH8_9CAUD      RKLLINSLYGGLGNVWFRYYDLRNATSITLFGQCAIQWIERKINE---------------       601
tr|A0A0B5A2H2|A0A0B5A2H2_9CAUD      RKSLINSLYGALGNIYFRYYDLRNASAITLFGQMAIQWIERKINE---------------       601
sp|Q38087|DPOL_BPR69                RKLLINSLYGALGNVWFRYYDLRNATAITTFGQMALQWIERKVNE---------------       603
tr|A0A1Z1LY62|A0A1Z1LY62_9CAUD      RKLLINSLYGALGNVWFRYYDLRNASAITLFGQMAIQWIERKINE---------------       602
tr|A0A1S7DLM5|A0A1S7DLM5_MCV2       YKVVANSVYGLMGFYNSSLYSYSSAKCCTTIGRVMITYLDRVVDGATLCAGVLRLASEPR       716
tr|Q6TUX3|Q6TUX3_YMTV5              YKIVANSVYGLMGFRNSVLYSYASAKTCTAIGRMMILYLNSVLDGSKINSGKFTFAKLPL       720
sp|P0DOO5|DPOL_VAR67                YKIIANSVYGLMGFRNSALYSYASAKSCTSIGRRMILYLESVLNGAELSNGMLRFANPLS       718
sp|P0DOO6|DPOL_VARV                 YKIIANSVYGLMGFRNSALYSYASAKSCTSIGRRMILYLESVLNGAELSNGMLRFANPLS       718
sp|A0A7H0DN44|DPOL_MONPV            YKIVANSVYGLMGFRNSALYSYASAKSCTSIGRRMILYLESVLNGAELSNGMLRFANTLS       719
sp|O57191|DPOL_VACCA                YKIVANSVYGLMGFRNSALYSYASAKSCTSIGRRMILYLESVLNGAELSNGMLRFANPLS       719
tr|A0A287NEC0|A0A287NEC0_HORVV      LKISANSVYGFTGATVGQLPCLEISSSVTSYGRQMIEHTKKLVED---------------       761
tr|A0A3B6JHK9|A0A3B6JHK9_WHEAT      LKISANSVYGFTGATVGQLPCLEISSSVTSYGRQMIEHTKKLVED---------------       741
tr|A0A1D6QLT8|A0A1D6QLT8_MAIZE      LKISANSVYGFTGATVGQLPCLEISSSVTSYGRQMIEHTKKLVED---------------       741
sp|Q9LRE6|DPOD1_ORYSJ               LKISANSVYGFTGATVGQLPCLEISSSVTSYGRQMIEHTKKLVED---------------       743
sp|Q9LVN7|DPOD1_ARATH               LKISANSVYGFTGATVGQLPCLEISSSVTSYGRQMIEQTKKLVED---------------       735
tr|A0A078I2E2|A0A078I2E2_BRANA      LKISANSVYGFTGATVGQLPCLEISSSVTSYGRQMIEQTKKFVED---------------       730
tr|D0VEW7|D0VEW7_XENLA              LKVSANSVYGFTGAQVGKLPCLEISQSVTGFGRQMIEKTKQLVES---------------       741
tr|G3V8M1|G3V8M1_RAT                LKVSANSVYGFTGAQVGKLPCLEISQSVTGFGRQMIEKTKQLVET---------------       733
sp|P52431|DPOD1_MOUSE               LKVSANSVYGFTGAQVGKLPCLEISQSVTGFGRQMIEKTKQLVES---------------       735
sp|P28340|DPOD1_HUMAN               LKVSANSVYGFTGAQVGKLPCLEISQSVTGFGRQMIEKTKQLVES---------------       737
tr|F7DXU3|F7DXU3_HORSE              LKVSANSVYGFTGAQVGKLPCLEISQSVTGFGRQMIERTKQLVES---------------       737
tr|M3VUJ4|M3VUJ4_FELCA              LKVSANSVYGFTGAQVGKLPCLEISQSVTGFGRQMIEKTKQLVES---------------       737
tr|A0A5G2QET9|A0A5G2QET9_PIG        LKVSANSVYGFTGAQVGKLPCLEISQSVTGFGRQMIEKTKQLVES---------------       757
tr|E1BNZ6|E1BNZ6_BOVIN              LKVSANSVYGFTGAQVGRLPCLEISQSVTGFGRQMIEKTKQLVET---------------       736
                                     *   *:.**  *           :   *  *:  :      :
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tr|A8ALP2|A8ALP2_CITK8              ----------------------EA-QGYDVIYGDTDSTFVWLKGAHSEDEAARIG-RELV       570
tr|D2TGG5|D2TGG5_CITRI              ----------------------EA-QGYDVIYGDTDSTFVWLKRARSEEEAAQIG-RSLV       570
tr|A0A5Y2S1M3|A0A5Y2S1M3_SALER      ----------------------EA-QGYDVIYGDTDSTFVWLRRAHSEADAAKIG-HMLV       570
tr|A0A2B7LUW5|A0A2B7LUW5_9ESCH      ----------------------EA-QGYDVIYGDTDSTFVWLKGAHCEEEAAKIG-RALV       570
tr|B7LVT1|B7LVT1_ESCF3              ----------------------EA-QGYDVIYGDTDSTFVWLKGAHSEEEAAKIG-RALV       570
tr|A0A6N3R803|A0A6N3R803_SHIFL      ----------------------EA-QGYDVIYGDTDSTFVWLKGAHSEEEAAKIG-RALV       570
sp|P21189|DPO2_ECOLI                ----------------------EA-QGYDVIYGDTDSTFVWLKGAHSEEEAAKIG-RALV       570
tr|A0A3P6LPK6|A0A3P6LPK6_SHIDY      ----------------------EA-QGYDVIYGDTDSTFVWLKGAHSEEEAAKIG-RALV       570
tr|A0A0K0QSA0|A0A0K0QSA0_9CAUD      ----------------YLNQLCNTTDYAYVRYCDTDSIYVCMDNVIEK-----VGGESKF       636
tr|A0A1W5P0A4|A0A1W5P0A4_9CAUD      ----------------YLNELCNTTDYAYVRYCDTDSIYVCMDNVIAK-----VGGESKF       636
tr|A0A7U3VGB5|A0A7U3VGB5_9CAUD      ----------------YLNELCGTTDHPYVIYGDTDSLYIELSPLIEK-----VG-IDKF       639
tr|A0A5Q2F6H2|A0A5Q2F6H2_9CAUD      ----------------YLNKVCGTEGHSFVVAGDTDSIYVCVDKVIEK-----VG-LERF       639
tr|A0A2K9VME2|A0A2K9VME2_9CAUD      ----------------YLNKVCGTNGEDFIAAGDTDSVYVCVDKVIEK-----VG-LDRF       687
tr|A0A249XWD5|A0A249XWD5_9CAUD      ----------------YLNKVCGTNGEDFIAAGDTDSVYVCVDKVIEK-----VG-LDRF       638
sp|P04415|DPOL_BPT4                 ----------------YLNKVCGTNDEDFIAAGDTDSVYVCVDKVIEK-----VG-LDRF       638
tr|A0A2U7NJH8|A0A2U7NJH8_9CAUD      ----------------YLNGVVGTTNHKYVIYGDTDSVYICIDPLVNK-----VG-EHKF       639
tr|A0A0B5A2H2|A0A0B5A2H2_9CAUD      ----------------YLNKTIGTNNFNYVIAGDTDSVYVCADKLIEK-----VG-EDKF       639
sp|Q38087|DPOL_BPR69                ----------------YLNEVCGTEGEAFVLYGDTDSIYVSADKIIDK-----VG-ESKF       641
tr|A0A1Z1LY62|A0A1Z1LY62_9CAUD      ----------------YMNKVVGLEDHKFVIAGDTDSVYICVDKLIDK-----VG-EDKF       640
tr|A0A1S7DLM5|A0A1S7DLM5_MCV2       NPLLASAPPRARDVDVSAALGHELELRFRSVYGDTDSIFLELNLR-EVQTTLAVA-----       770
tr|Q6TUX3|Q6TUX3_YMTV5              NPFFEDGRYV--TLNTDTGVDKHYNFVFKTVYGDTDSVFLEMNTQ-DVDTSIIIA-----       772
sp|P0DOO5|DPOL_VAR67                NPFYMDDRDI--NPIVKTSLPIDYRFRFRSVYGDTDSVFTEIDSQ-DVDKSIEIA-----       770
sp|P0DOO6|DPOL_VARV                 NPFYMDDRDI--NPIVKTSLPIDYRFRFRSVYGDTDSVFTEIDSQ-DVDKSIEIA-----       770
sp|A0A7H0DN44|DPOL_MONPV            NPFYMDDRDI--NPIVKTSLPIDYRFRFRSVYGDTDSVFTEIDSQ-DVDKSIEIA-----       771
sp|O57191|DPOL_VACCA                NPFYMDDRDI--NPIVKTSLPIDYRFRFRSVYGDTDSVFTEIDSQ-DVDKSIEIA-----       771
tr|A0A287NEC0|A0A287NEC0_HORVV      ----------------KFTTVGGYEHNAEVIYGDTDSVMVQFGVS-TVKDAMKLG-----       799
tr|A0A3B6JHK9|A0A3B6JHK9_WHEAT      ----------------KFTTLGGYEHNAEVIYGDTDSVMVQFGAS-TVEDAMKLG-----       779
tr|A0A1D6QLT8|A0A1D6QLT8_MAIZE      ----------------KFTTVGGYEHTAEVIYGDTDSVMVQFGVS-TVEDAMKLG-----       779
sp|Q9LRE6|DPOD1_ORYSJ               ----------------KFTTLGGYEHNAEVIYGDTDSVMVQFGVS-TVEDAMKLG-----       781
sp|Q9LVN7|DPOD1_ARATH               ----------------KFTTLGGYQYNAEVIYGDTDSVMVQFGVS-DVEAAMTLG-----       773
tr|A0A078I2E2|A0A078I2E2_BRANA      ----------------KFTTLGGYEYNAEVIYGDTDSVMVQFGVP-DVEAAMTLG-----       768
tr|D0VEW7|D0VEW7_XENLA              ----------------KYTLDNGYKADAKVIYGDTDSVMCKLGVQ-TVAEAMELG-----       779
tr|G3V8M1|G3V8M1_RAT                ----------------KYTLENGYDANAKVVYGDTDSVMCRFGVS-SVAEAMSLG-----       771
sp|P52431|DPOD1_MOUSE               ----------------KYTVENGYDANAKVVYGDTDSVMCRFGVS-SVAEAMSLG-----       773
sp|P28340|DPOD1_HUMAN               ----------------KYTVENGYSTSAKVVYGDTDSVMCRFGVS-SVAEAMALG-----       775
tr|F7DXU3|F7DXU3_HORSE              ----------------KYTTENGYSASAKVVYGDTDSVMCRFGVS-SVAEAMALG-----       775
tr|M3VUJ4|M3VUJ4_FELCA              ----------------KYTVENGYGTSAKVVYGDTDSVMCRFGVS-SVAEAMALG-----       775
tr|A0A5G2QET9|A0A5G2QET9_PIG        ----------------KYTVENGYGTSAKVVYGDTDSVMCRFGVS-SVAEAMALG-----       795
tr|E1BNZ6|E1BNZ6_BOVIN              ----------------KYTVENGYSTSAKVVYGDTDSVMCRFGVS-SVAEAMALG-----       774
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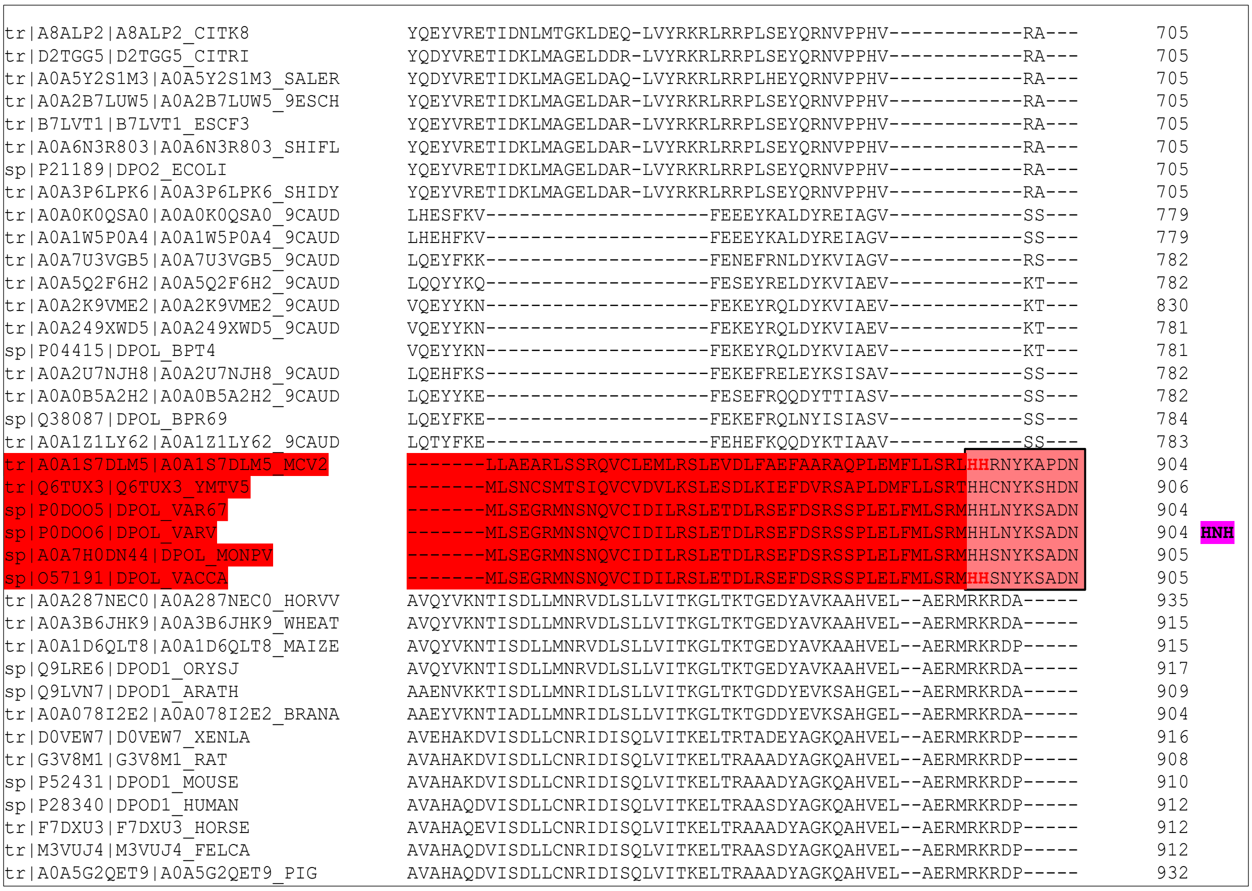

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tr|D2TGG5|D2TGG5_CITRI              YQDYVRETIDKLMAGELDDR-LVYRKRLRRPLSEYQRNVPPHV------------RA---       705
tr|A0A5Y2S1M3|A0A5Y2S1M3_SALER      YQDYVRETIDKLMAGELDAQ-LVYRKRLRRPLHEYQRNVPPHV------------RA---       705
tr|A0A2B7LUW5|A0A2B7LUW5_9ESCH      YQEYVRETIDKLMAGELDAR-LVYRKRLRRPLSEYQRNVPPHV------------RA---       705
tr|B7LVT1|B7LVT1_ESCF3              YQEYVRETIDKLMAGELDAR-LVYRKRLRRPLSEYQRNVPPHV------------RA---       705
tr|A0A6N3R803|A0A6N3R803_SHIFL      YQEYVRETIDKLMAGELDAR-LVYRKRLRRPLSEYQRNVPPHV------------RA---       705
sp|P21189|DPO2_ECOLI                YQEYVRETIDKLMAGELDAR-LVYRKRLRRPLSEYQRNVPPHV------------RA---       705
tr|A0A3P6LPK6|A0A3P6LPK6_SHIDY      YQEYVRETIDKLMAGELDAR-LVYRKRLRRPLSEYQRNVPPHV------------RA---       705
tr|A0A0K0QSA0|A0A0K0QSA0_9CAUD      LHESFKV--------------------FEEEYKALDYREIAGV------------SS---       779
tr|A0A1W5P0A4|A0A1W5P0A4_9CAUD      LHEHFKV--------------------FEEEYKALDYREIAGV------------SS---       779
tr|A0A7U3VGB5|A0A7U3VGB5_9CAUD      LQEYFKK--------------------FENEFRNLDYKVIAGV------------RS---       782
tr|A0A5Q2F6H2|A0A5Q2F6H2_9CAUD      LQQYYKQ--------------------FESEYRELDYKVIAEV------------KT---       782
tr|A0A2K9VME2|A0A2K9VME2_9CAUD      VQEYYKN--------------------FEKEYRQLDYKVIAEV------------KT---       830
tr|A0A249XWD5|A0A249XWD5_9CAUD      VQEYYKN--------------------FEKEYRQLDYKVIAEV------------KT---       781
sp|P04415|DPOL_BPT4                 VQEYYKN--------------------FEKEYRQLDYKVIAEV------------KT---       781
tr|A0A2U7NJH8|A0A2U7NJH8_9CAUD      LQEHFKS--------------------FEKEFRELEYKSISAV------------SS---       782
tr|A0A0B5A2H2|A0A0B5A2H2_9CAUD      LQEYYKE--------------------FESEFRQQDYTTIASV------------SS---       782
sp|Q38087|DPOL_BPR69                LQEYFKE--------------------FEKEFRQLNYISIASV------------SS---       784
tr|A0A1Z1LY62|A0A1Z1LY62_9CAUD      LQTYFKE--------------------FEHEFKQQDYKTIAAV------------SS---       783
tr|A0A1S7DLM5|A0A1S7DLM5_MCV2       -------LLAEARLSSRQVCLEMLRSLEVDLFAEFAARAQPLEMFLLSRLHHRNYKAPDN       904
tr|Q6TUX3|Q6TUX3_YMTV5              -------MLSNCSMTSIQVCVDVLKSLESDLKIEFDVRSAPLDMFLLSRTHHCNYKSHDN       906
sp|P0DOO5|DPOL_VAR67                -------MLSEGRMNSNQVCIDILRSLETDLRSEFDSRSSPLELFMLSRMHHLNYKSADN       904
sp|P0DOO6|DPOL_VARV                 -------MLSEGRMNSNQVCIDILRSLETDLRSEFDSRSSPLELFMLSRMHHLNYKSADN       904
sp|A0A7H0DN44|DPOL_MONPV            -------MLSEGRMNSNQVCIDILRSLETDLRSEFDSRSSPLELFMLSRMHHSNYKSADN       905
sp|O57191|DPOL_VACCA                -------MLSEGRMNSNQVCIDILRSLETDLRSEFDSRSSPLELFMLSRMHHSNYKSADN       905
tr|A0A287NEC0|A0A287NEC0_HORVV      AVQYVKNTISDLLMNRVDLSLLVITKGLTKTGEDYAVKAAHVEL--AERMRKRDA-----       935
tr|A0A3B6JHK9|A0A3B6JHK9_WHEAT      AVQYVKNTISDLLMNRVDLSLLVITKGLTKTGEDYAVKAAHVEL--AERMRKRDA-----       915
tr|A0A1D6QLT8|A0A1D6QLT8_MAIZE      AVQYVKNTISDLLMNRVDLSLLVITKGLTKTGEDYAVKAAHVEL--AERMRKRDP-----       915
sp|Q9LRE6|DPOD1_ORYSJ               AVQYVKNTISDLLMNRVDLSLLVITKGLTKTGEDYAVKAAHVEL--AERMRKRDA-----       917
sp|Q9LVN7|DPOD1_ARATH               AAENVKKTISDLLMNRIDLSLLVITKGLTKTGDDYEVKSAHGEL--AERMRKRDA-----       909
tr|A0A078I2E2|A0A078I2E2_BRANA      AAEYVKNTIADLLMNRIDLSLLVITKGLTKTGDDYEVKSAHGEL--AERMRKRDA-----       904
tr|D0VEW7|D0VEW7_XENLA              AVEHAKDVISDLLCNRIDISQLVITKELTRTADEYAGKQAHVEL--AERMRKRDP-----       916
tr|G3V8M1|G3V8M1_RAT                AVAHAKDVISDLLCNRIDISQLVITKELTRAAADYAGKQAHVEL--AERMRKRDP-----       908
sp|P52431|DPOD1_MOUSE               AVAHAKDVISDLLCNRIDISQLVITKELTRAAADYAGKQAHVEL--AERMRKRDP-----       910
sp|P28340|DPOD1_HUMAN               AVAHAQDVISDLLCNRIDISQLVITKELTRAASDYAGKQAHVEL--AERMRKRDP-----       912
tr|F7DXU3|F7DXU3_HORSE              AVAHAQEVISDLLCNRIDISQLVITKELTRAAADYAGKQAHVEL--AERMRKRDP-----       912
tr|M3VUJ4|M3VUJ4_FELCA              AVAHAQDVISDLLCNRIDISQLVITKELTRAASDYAGKQAHVEL--AERMRKRDP-----       912
tr|A0A5G2QET9|A0A5G2QET9_PIG        AVAHAQDVISDLLCNRIDISQLVITKELTRAAADYAGKQAHVEL--AERMRKRDP-----       932
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tr|E1BNZ6|E1BNZ6_BOVIN              AVAHAQDVISDLLCNRIDISQLVITKELTRAAADYAGKQAHVEL--AERMRKRDP-----    911
tr|A8ALP2|A8ALP2_CITK8              --ARLADEQ------NIKLGRPAQYQNRGTIKYVWTTNGP--------------------    737
tr|D2TGG5|D2TGG5_CITRI              --ARLADEE------NLKRGRPAQYQNRGTIQYLWTVNGP--------------------    737
tr|A0A5Y2S1M3|A0A5Y2S1M3_SALER      --ARLADEQ------NLKRGRPAQYQNRGAIKYVWTVNGP--------------------    737
tr|A0A2B7LUW5|A0A2B7LUW5_9ESCH      --ARLADEE------NQKRGRPLQYQNRGTIKYVWTTNGP--------------------    737
tr|B7LVT1|B7LVT1_ESCF3              --ARLADEE------NQKRGRPLQYQNRGTIKYVWTTNGP--------------------    737
tr|A0A6N3R803|A0A6N3R803_SHIFL      --ARLADEE------NQKRGRPLQYQNRGTIKYVWTTNGP--------------------    737
sp|P21189|DPO2_ECOLI                --ARLADEE------NQKRGRPLQYQNRGTIKYVWTTNGP--------------------    737
tr|A0A3P6LPK6|A0A3P6LPK6_SHIDY      --ARLADEE------NQKRGRPLQYQNRGTIKYVWTTNGP--------------------    737
tr|A0A0K0QSA0|A0A0K0QSA0_9CAUD      --ANNITKYNDG---TGHPIKGTPNHIKGVLFFNRLTRGI--QGITQIMEGEKVMVLPLR    832
tr|A0A1W5P0A4|A0A1W5P0A4_9CAUD      --ANNISKYNDG---AGFPIKGTPNHIKGVLFFNRHTKGI--QGITPIMEGEKVMVLPLR    832
tr|A0A7U3VGB5|A0A7U3VGB5_9CAUD      --ANNIAKYDV----NGFPGLKCPSHVRGVLTYRRAIKKY--DNLPDISEGEKVMILPLK    834
tr|A0A5Q2F6H2|A0A5Q2F6H2_9CAUD      --ANNIGKYDDG---AGYPDKGTPYHVKGALAYNRATAGF--EGITPIMEGEKVMVIPLR    835
tr|A0A2K9VME2|A0A2K9VME2_9CAUD      --ANDIAKYDD----KGWPGFKCPFHIRGVLTYRRAVSGL---GVAPILDGNKVMVLPLR    881
tr|A0A249XWD5|A0A249XWD5_9CAUD      --ANDIAKYDD----KGWPGFKCPFHIRGVLTYRRAVSGL---GVAPILDGNKVMVLPLR    832
sp|P04415|DPOL_BPT4                 --ANDIAKYDD----KGWPGFKCPFHIRGVLTYRRAVSGL---GVAPILDGNKVMVLPLR    832
tr|A0A2U7NJH8|A0A2U7NJH8_9CAUD      --ANNIAKYDV----DGFPGYKCPYHIRGILTYHRAINGT---YAPRIADGDKVMVLPLR    833
tr|A0A0B5A2H2|A0A0B5A2H2_9CAUD      --ANNIAKYDD----NGFPGFKCPSHIRGVLTYNRASKNV--DGAEAIVEGEKVMVLPLM    834
sp|Q38087|DPOL_BPR69                --ANNIAKYDV----GGFPGPKCPFHIRGILTYNRAIKGN--IDAPQVVEGEKVYVLPLR    836
tr|A0A1Z1LY62|A0A1Z1LY62_9CAUD      --ANNIMKYDV----GGYPGPKCPYHIRGILTYNRATKGM--PNVTAITEGEKVMVLPLR    835
tr|A0A1S7DLM5|A0A1S7DLM5_MCV2       PNVELVNRYNRENLEPIELGERYYYAYICASELPWQLAVANVRNHERIV--DASYVLP--    960
tr|Q6TUX3|Q6TUX3_YMTV5              PNMFLVNEYNNNNAEIIEIGERYFFAYICPSKYPWQKKLVNIKTYERII--DRRFKLN--    962
sp|P0DOO5|DPOL_VAR67                PNMYLVTEYNKNNPETIELGERYYFAYICPANVPWTKKLVNIKTYETII--DRSFKLG--    960 HNH
sp|P0DOO6|DPOL_VARV                 PNMYLVTEYNKNNPETIELGERYYFAYICPANVPWTKKLVNIKTYETII--DRSFKLG--    960
sp|A0A7H0DN44|DPOL_MONPV            PNMYLVTEYNKNNPETIELGERYYFAYICPANVPWTKKLVNIKTYETII--DRSFKLG--    961
sp|O57191|DPOL_VACCA                PNMYLVTEYNKNNPETIELGERYYFAYICPANVPWTKKLVNIKTYETII--DRSFKLG--    961
tr|A0A287NEC0|A0A287NEC0_HORVV      -------------ATAPTVGDRVPYVIIKAA--------KGAKAYEKSE--DPIYVLD--    970
tr|A0A3B6JHK9|A0A3B6JHK9_WHEAT      -------------ATAPTVGDRVPYVIVKAA--------KGAKAYEKSE--DPIYVLD--    950
tr|A0A1D6QLT8|A0A1D6QLT8_MAIZE      -------------ATAPTVGDRVPYVIIKAA--------KGAKAYEKSE--DPIYVLD--    950
sp|Q9LRE6|DPOD1_ORYSJ               -------------ATAPTVGDRVPYVIIKAA--------KGAKAYERSE--DPIYVLD--    952
sp|Q9LVN7|DPOD1_ARATH               -------------ATAPNVGDRVPYVIIKAA--------KGAKAYERSE--DPIYVLQ--    944
tr|A0A078I2E2|A0A078I2E2_BRANA      -------------ATAPNVGDRVPYVIITAA--------KGAKGYEKSE--DPIYVLE--    939
tr|D0VEW7|D0VEW7_XENLA              -------------GSAPNLGDRVPYVIIGAA--------KGVAAYMKSE--DPIYVLE--    951
tr|G3V8M1|G3V8M1_RAT                -------------GSAPNLGDRVPYVIIGAA--------KGVAAYMKSE--DPLFVLE--    943
sp|P52431|DPOD1_MOUSE               -------------GSAPSLGDRVPYVIIGAA--------KGVAAYMKSE--DPLFVLE--    945
sp|P28340|DPOD1_HUMAN               -------------GSAPSLGDRVPYVIISAA--------KGVAAYMKSE--DPLFVLE--    947
tr|F7DXU3|F7DXU3_HORSE              -------------GSAPSLGDRVPYVIIGAA--------KGVAAYMKSE--DPLFVLE--    947
tr|M3VUJ4|M3VUJ4_FELCA              -------------GSAPSLGDRVPYVIIGAA--------KGVAAYMKSE--DPLFVLE--    947
tr|A0A5G2QET9|A0A5G2QET9_PIG        -------------GSAPSLGDRVPYVIISAA--------KGVAAYMKSE--DPLFVLE--    967
tr|E1BNZ6|E1BNZ6_BOVIN              -------------GSAPSLGDRVPYVIISAA--------KGVAAYMKSE--DPLFVLE--    946
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tr|A8ALP2|A8ALP2_CITK8              ----------QPVAEGILPFIDDNFA---------TLLTGQL------------------    780
tr|D2TGG5|D2TGG5_CITRI              ----------QPVAEGILPFIDDNFA---------TLLTGQL------------------    780
tr|A0A5Y2S1M3|A0A5Y2S1M3_SALER      ----------QPVAEGILPFIEDNFA---------TLLTGQL------------------    780
tr|A0A2B7LUW5|A0A2B7LUW5_9ESCH      ----------QPVAEGILPFIEDNFA---------TLMTGQL------------------    780
tr|B7LVT1|B7LVT1_ESCF3              ----------QPVAEGILPFIEDNFA---------TLMTGQL------------------    780
tr|A0A6N3R803|A0A6N3R803_SHIFL      ----------QPVAEGILPFIEDNFA---------TLMTGQL------------------    780
sp|P21189|DPO2_ECOLI                ----------QPVAEGILPFIEDNFA---------TLMTGQL------------------    780
tr|A0A3P6LPK6|A0A3P6LPK6_SHIDY      ----------QPVAEGILPFIEDNFA---------TLMTGQL------------------    780
tr|A0A0K0QSA0|A0A0K0QSA0_9CAUD      ---------------------EKHVI---------SPLKNITEACKI--------DYEKR    890
tr|A0A1W5P0A4|A0A1W5P0A4_9CAUD      ---------------------EKHVI---------SPLQNITEACKI--------DYEKR    890
tr|A0A7U3VGB5|A0A7U3VGB5_9CAUD      ---------------------GKTYK---------KPLEGMCESAGM--------QAEKR    892
tr|A0A5Q2F6H2|A0A5Q2F6H2_9CAUD      ---------------------QKSFV---------KPLTGMSEAAGL--------DYEEK    893
tr|A0A2K9VME2|A0A2K9VME2_9CAUD      ---------------------QKSFV---------KPLAGMCESAGM--------DYEEK    939
tr|A0A249XWD5|A0A249XWD5_9CAUD      ---------------------QKSFV---------KPLAGMCESAGM--------DYEEK    890
sp|P04415|DPOL_BPT4                 ---------------------QKSFV---------KPLAGMCESAGM--------DYEEK    890
tr|A0A2U7NJH8|A0A2U7NJH8_9CAUD      ---------------------EKTFV---------KPLAALTEACKI--------DYEKR    891
tr|A0A0B5A2H2|A0A0B5A2H2_9CAUD      ---------------------NKTFV---------KPLESFTTAAEL--------HYEKR    892
sp|Q38087|DPOL_BPR69                ---------------------EKTFI---------KPLEGFTSAAKL--------DYEKK    894
tr|A0A1Z1LY62|A0A1Z1LY62_9CAUD      ---------------------NKTFV---------KPLTSFTEAAKI--------DYEKK    893
tr|A0A1S7DLM5|A0A1S7DLM5_MCV2       DNKPLCAEFFTRLFGVRPVFSN--------------------------------------    1004
tr|Q6TUX3|Q6TUX3_YMTV5              DNKVLSTSFFERMFGTKPIFYS--------------------------------------    1006
sp|P0DOO5|DPOL_VAR67                DNKVLCISFFERMFGSRPTFYEA-------------------------------------    1005
sp|P0DOO6|DPOL_VARV                 DNKVLCISFFERMFGSRPTFYEA-------------------------------------    1005
sp|A0A7H0DN44|DPOL_MONPV            DNKVLCISFFQRMFGSRPTFYEA-------------------------------------    1006
sp|O57191|DPOL_VACCA                DNKVLCISFFERMFGSKPTFYEA-----------------------CysA--------------    1006
tr|A0A287NEC0|A0A287NEC0_HORVV      GSHTRAVSISTPSNSGIMKFAKKQLTCLGCKAVISGPNQTLCSHCKGREAELYCKTVANV    1066
tr|A0A3B6JHK9|A0A3B6JHK9_WHEAT      GSHTRAVSISTPSNSGIMKFAKKQLTCLGCKAVISGPNQTLCSHCKGREAELYCKTVANV    1046
tr|A0A1D6QLT8|A0A1D6QLT8_MAIZE      GSHTRSVSISTPSNSGIMKFAKKQLTCLGCKAVISGASQTLCSHCKGREAELYCKTVANV    1046
sp|Q9LRE6|DPOD1_ORYSJ               GSHTRAVSISTPSNSGIMKFAKKQLTCLGCKAVISGSNQTLCFHCKGREAELYCKTVGNV    1048
sp|Q9LVN7|DPOD1_ARATH               GSHTRSISITTPSNSGIMKFAKKQLSCVGCKVPIS--NGTLCASCKGREAELYCKNVSQV    1038
tr|A0A078I2E2|A0A078I2E2_BRANA      GDHMRSISITTPSNSGIMRFAKKQLSCVGCKVPIS--TGTLCARCKGREAELYCKNVSQV    1033
tr|D0VEW7|D0VEW7_XENLA              GEHTRCKTVLTAKVGGLMAFAKKRSTCIGCKATLNH-DGAVCNYCKQRESELLQKEISQL    1048
tr|G3V8M1|G3V8M1_RAT                GDHTRCKTVLTSKVGGLLAFTKRRNSCIGCRSVIDH-QGAVCKFCQPRESELYQKEVSHL    1040
sp|P52431|DPOD1_MOUSE               GDHTRCKTVLTSKVGGLLAFTKRRNCCIGCRSVIDH-QGAVCKFCQPRESELYQKEVSHL    1042
sp|P28340|DPOD1_HUMAN               GDHTRCKTVLTGKVGGLLAFAKRRNCCIGCRTVLSH-QGAVCEFCQPRESELYQKEVSHL    1044
tr|F7DXU3|F7DXU3_HORSE              GDHTRCKTVLTGKVGGLLAFAQRRSCCIGCRTVLSH-QGAVCKFCQPRESELYQKEVSHL    1044
tr|M3VUJ4|M3VUJ4_FELCA              GDHTRCKTVLTGKVGGLLAFAKRHSCCIGCRTVLGH-QGAVCKFCQPRESELYQKEVSHL    1044
tr|A0A5G2QET9|A0A5G2QET9_PIG        GDHTRCKTVLTGKVGGLLAFAKRRNCCIGCRTVLSH-QGAVCKFCQPRESELYQKEVSHL    1064
tr|E1BNZ6|E1BNZ6_BOVIN              GDHTRCKTVLTGKVGGLLAFAKRRNCCIGCRTVLSH-QGAVCKFCQPRESELYQKEVSHL    1043
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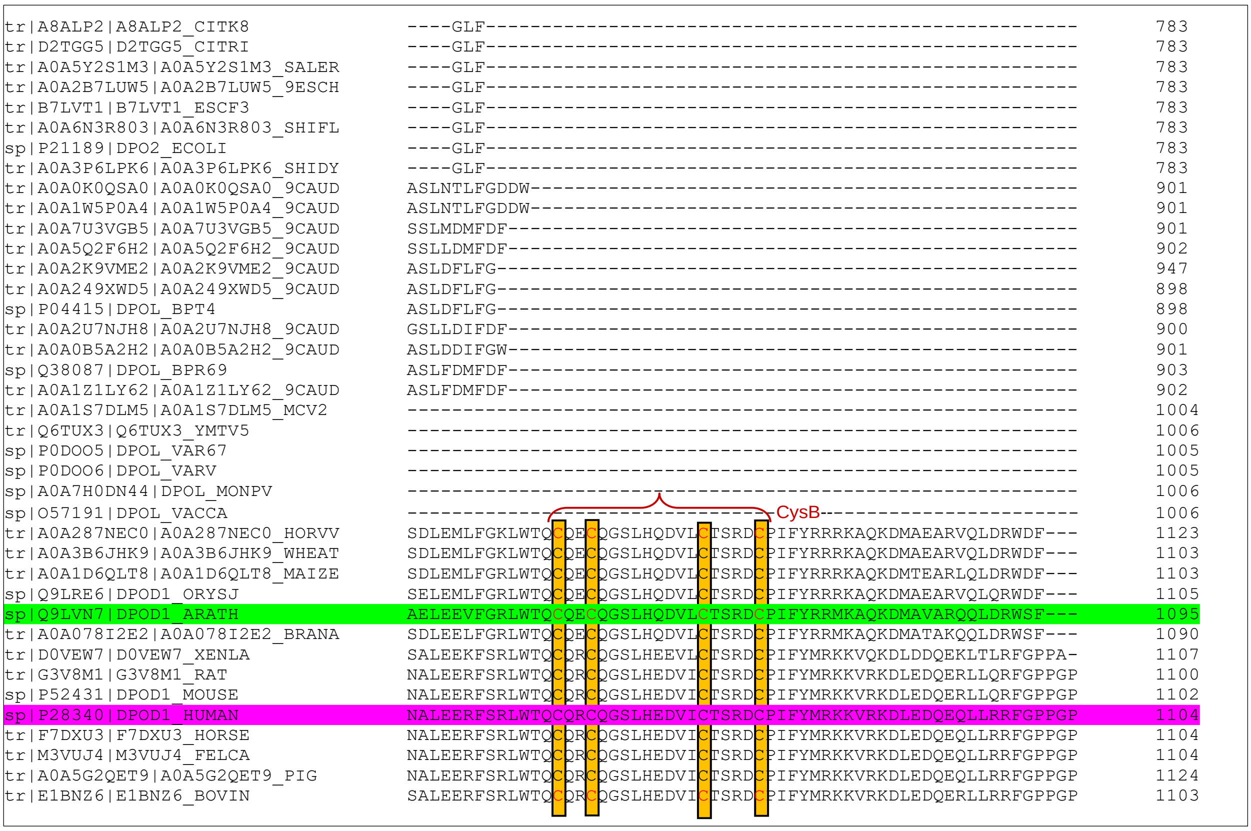

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tr|D2TGG5|D2TGG5_CITRI                ----GLF-----------------------------------------------------      783
tr|A0A5Y2S1M3|A0A5Y2S1M3_SALER        ----GLF-----------------------------------------------------      783
tr|A0A2B7LUW5|A0A2B7LUW5_9ESCH        ----GLF-----------------------------------------------------      783
tr|B7LVT1|B7LVT1_ESCF3                ----GLF-----------------------------------------------------      783
tr|A0A6N3R803|A0A6N3R803_SHIFL        ----GLF-----------------------------------------------------      783
sp|P21189|DPO2_ECOLI                  ----GLF-----------------------------------------------------      783
tr|A0A3P6LPK6|A0A3P6LPK6_SHIDY        ----GLF-----------------------------------------------------      783
tr|A0A0K0QSA0|A0A0K0QSA0_9CAUD        ASLNTLFGDDW-------------------------------------------------      901
tr|A0A1W5P0A4|A0A1W5P0A4_9CAUD        ASLNTLFGDDW-------------------------------------------------      901
tr|A0A7U3VGB5|A0A7U3VGB5_9CAUD        SSLMDMFDF---------------------------------------------------      901
tr|A0A5Q2F6H2|A0A5Q2F6H2_9CAUD        SSLLDMFDF---------------------------------------------------      902
tr|A0A2K9VME2|A0A2K9VME2_9CAUD        ASLDFLFG----------------------------------------------------      947
tr|A0A249XWD5|A0A249XWD5_9CAUD        ASLDFLFG----------------------------------------------------      898
sp|P04415|DPOL_BPT4                   ASLDFLFG----------------------------------------------------      898
tr|A0A2U7NJH8|A0A2U7NJH8_9CAUD        GSLLDIFDF---------------------------------------------------      900
tr|A0A0B5A2H2|A0A0B5A2H2_9CAUD        ASLDDIFGW---------------------------------------------------      901
sp|Q38087|DPOL_BPR69                  ASLFDMFDF---------------------------------------------------      903
tr|A0A1Z1LY62|A0A1Z1LY62_9CAUD        ASLFDMFDF---------------------------------------------------      902
tr|A0A1S7DLM5|A0A1S7DLM5_MCV2         ------------------------------------------------------------      1004
tr|Q6TUX3|Q6TUX3_YMTV5                ------------------------------------------------------------      1006
sp|P0DOO5|DPOL_VAR67                  ------------------------------------------------------------      1005
sp|P0DOO6|DPOL_VARV                   ------------------------------------------------------------      1005
sp|A0A7H0DN44|DPOL_MONPV              ------------------------------------------------------------      1006
sp|O57191|DPOL_VACCA                  ------------------------------------------------------------      1006
tr|A0A287NEC0|A0A287NEC0_HORVV        SDLEMLFGKLWTQCQECQGSLHQDVLCTSRDCPIFYRRRKAQKDMAEARVQLDRWDF---      1123
tr|A0A3B6JHK9|A0A3B6JHK9_WHEAT        SDLEMLFGKLWTQCQECQGSLHQDVLCTSRDCPIFYRRRKAQKDMAEARVQLDRWDF---      1103
tr|A0A1D6QLT8|A0A1D6QLT8_MAIZE        SDLEMLFGRLWTQCQECQGSLHQDVLCTSRDCPIFYRRRKAQKDMTEARLQLDRWDF---      1103
sp|Q9LRE6|DPOD1_ORYSJ                 SELEMLFGRLWTQCQECQGSLHQDVLCTSRDCPIFYRRRKAQKDMAEARVQLQRWDF---      1105
sp|Q9LVN7|DPOD1_ARATH                 AELEEVFGRLWTQCQECQGSLHQDVLCTSRDCPIFYRRMKAQKDMAVARQQLDRWSF---      1095
tr|A0A078I2E2|A0A078I2E2_BRANA        SDLEELFGRLWTQCQECQGSLHQDVLCTSRDCPIFYRRMKAQKDMATAKQQLDRWSF---      1090
tr|D0VEW7|D0VEW7_XENLA                SALEEKFSRLWTQCQRCQGSLHEEVLCTSRDCPIFYMRKKVQKDLDDQEKLTLRFGPPA-      1107
tr|G3V8M1|G3V8M1_RAT                  NALEERFSRLWTQCQRCQGSLHEDVICTSRDCPIFYMRKKVRKDLEDQERLLQRFGPPGP      1100
sp|P52431|DPOD1_MOUSE                 NALEERFSRLWTQCQRCQGSLHEDVICTSRDCPIFYMRKKVRKDLEDQERLLQRFGPPGP      1102
sp|P28340|DPOD1_HUMAN                 NALEERFSRLWTQCQRCQGSLHEDVICTSRDCPIFYMRKKVRKDLEDQEQLLRRFGPPGP      1104
tr|F7DXU3|F7DXU3_HORSE                NALEERFSRLWTQCQRCQGSLHEDVICTSRDCPIFYMRKKVRKDLEDQEQLLRRFGPPGP      1104
tr|M3VUJ4|M3VUJ4_FELCA                NALEERFSRLWTQCQRCQGSLHEDVICTSRDCPIFYMRKKVRKDLEDQEQLLRRFGPPGP      1104
tr|A0A5G2QET9|A0A5G2QET9_PIG          NALEERFSRLWTQCQRCQGSLHEDVICTSRDCPIFYMRKKVRKDLEDQEQLLRRFGPPGP      1124
tr|E1BNZ6|E1BNZ6_BOVIN                SALEERFSRLWTQCQRCQGSLHEDVICTSRDCPIFYMRKKVRKDLEDQERLLRRFGPPGP      1103
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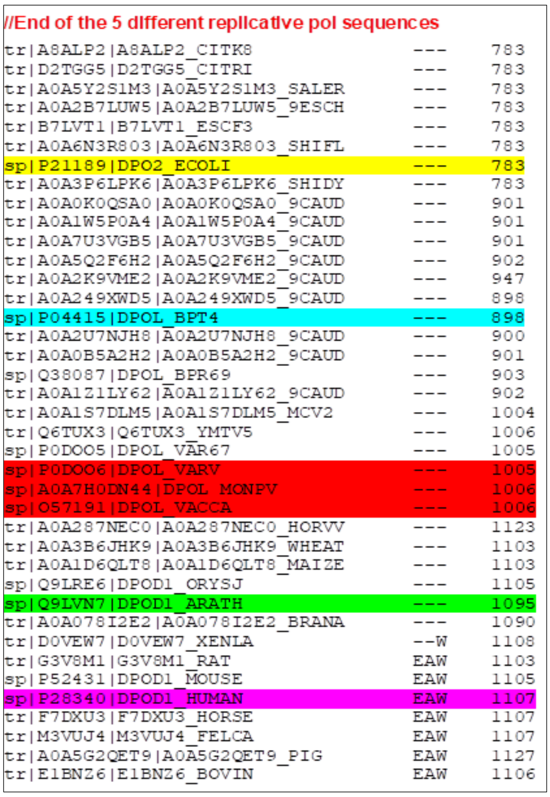

//End of the 5 different replicative pol sequences

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tr|A8ALP2|A8ALP2_CITK8                ---      783
tr|D2TGG5|D2TGG5_CITRI                ---      783
tr|A0A5Y2S1M3|A0A5Y2S1M3_SALER        ---      783
tr|A0A2B7LUW5|A0A2B7LUW5_9ESCH        ---      783
tr|B7LVT1|B7LVT1_ESCF3                ---      783
tr|A0A6N3R803|A0A6N3R803_SHIFL        ---      783
sp|P21189|DPO2_ECOLI                  ---      783
tr|A0A3P6LPK6|A0A3P6LPK6_SHIDY        ---      783
tr|A0A0K0QSA0|A0A0K0QSA0_9CAUD        ---      901
tr|A0A1W5P0A4|A0A1W5P0A4_9CAUD        ---      901
tr|A0A7U3VGB5|A0A7U3VGB5_9CAUD        ---      901
tr|A0A5Q2F6H2|A0A5Q2F6H2_9CAUD        ---      902
tr|A0A2K9VME2|A0A2K9VME2_9CAUD        ---      947
tr|A0A249XWD5|A0A249XWD5_9CAUD        ---      898
sp|P04415|DPOL_BPT4                   ---      898
tr|A0A2U7NJH8|A0A2U7NJH8_9CAUD        ---      900
tr|A0A0B5A2H2|A0A0B5A2H2_9CAUD        ---      901
sp|Q38087|DPOL_BPR69                  ---      903
tr|A0A1Z1LY62|A0A1Z1LY62_9CAUD        ---      902
tr|A0A1S7DLM5|A0A1S7DLM5_MCV2         ---      1004
tr|Q6TUX3|Q6TUX3_YMTV5                ---      1006
sp|P0DOO5|DPOL_VAR67                  ---      1005
sp|P0DOO6|DPOL_VARV                   ---      1005
sp|A0A7H0DN44|DPOL_MONPV              ---      1006
sp|O57191|DPOL_VACCA                  ---      1006
tr|A0A287NEC0|A0A287NEC0_HORVV        ---      1123
tr|A0A3B6JHK9|A0A3B6JHK9_WHEAT        ---      1103
tr|A0A1D6QLT8|A0A1D6QLT8_MAIZE        ---      1103
sp|Q9LRE6|DPOD1_ORYSJ                 ---      1105
sp|Q9LVN7|DPOD1_ARATH                 ---      1095
tr|A0A078I2E2|A0A078I2E2_BRANA        ---      1090
tr|D0VEW7|D0VEW7_XENLA                --W      1108
tr|G3V8M1|G3V8M1_RAT                  EAW      1103
sp|P52431|DPOD1_MOUSE                 EAW      1105
sp|P28340|DPOD1_HUMAN                 EAW      1107
tr|F7DXU3|F7DXU3_HORSE                EAW      1107
tr|M3VUJ4|M3VUJ4_FELCA                EAW      1107
tr|A0A5G2QET9|A0A5G2QET9_PIG          EAW      1127
tr|E1BNZ6|E1BNZ6_BOVIN                EAW      1106
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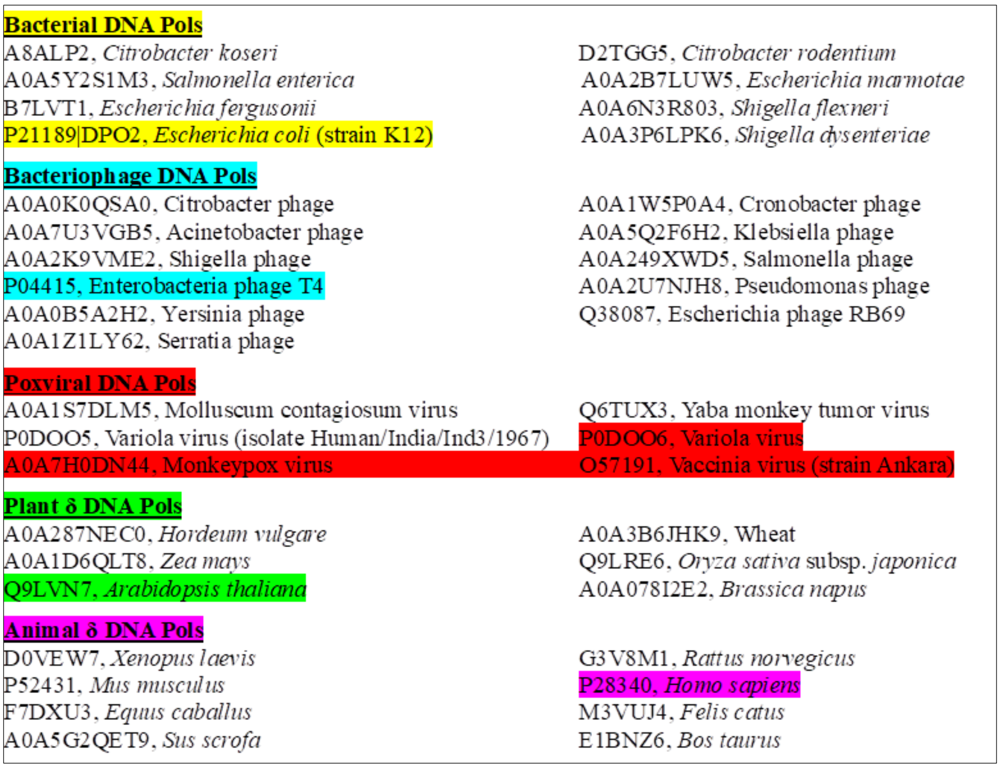

Bacterial DNA Pols

A8ALP2, *Citrobacter koseri*
A0A5Y2S1M3, *Salmonella enterica*
B7LVT1, *Escherichia fergusonii*
P21189|DPO2, *Escherichia coli* (strain K12)
D2TGG5, *Citrobacter rodentium*
A0A2B7LUW5, *Escherichia marmotae*
A0A6N3R803, *Shigella flexneri*
A0A3P6LPK6, *Shigella dysenteriae*

Bacteriophage DNA Pols

A0A0K0QSA0, Citrobacter phage
A0A7U3VGB5, Acinetobacter phage
A0A2K9VME2, Shigella phage
P04415, Enterobacteria phage T4
A0A0B5A2H2, Yersinia phage
A0A1Z1LY62, Serratia phage
A0A1W5P0A4, Cronobacter phage
A0A5Q2F6H2, Klebsiella phage
A0A249XWD5, Salmonella phage
A0A2U7NJH8, Pseudomonas phage
Q38087, Escherichia phage RB69

Poxviral DNA Pols

A0A1S7DLM5, Molluscum contagiosum virus
P0DOO5, Variola virus (isolate Human/India/Ind3/1967)
A0A7H0DN44, Monkeypox virus
Q6TUX3, Yaba monkey tumor virus
P0DOO6, Variola virus
O57191, Vaccinia virus (strain Ankara)

Plant δ DNA Pols

A0A287NEC0, *Hordeum vulgare*
A0A1D6QLT8, *Zea mays*
Q9LVN7, *Arabidopsis thaliana*
A0A3B6JHK9, Wheat
Q9LRE6, *Oryza sativa* subsp. *japonica*
A0A078I2E2, *Brassica napus*

Animal δ DNA Pols

D0VEW7, *Xenopus laevis*
P52431, *Mus musculus*
F7DXU3, *Equus caballus*
A0A5G2QET9, *Sus scrofa*
G3V8M1, *Rattus norvegicus*
P28340, *Homo sapiens*
M3VUJ4, *Felis catus*
E1BNZ6, *Bos taurus*

Figure 5 'Mix and match' MSA analysis of the replicative DNA pols from bacterial viruses, animal viruses (poxviruses), and from the replicative δ pols from plants and animals

4. Conclusions

The present study reveals both similarities and sharp differences between the replicative pols from poxviruses and other organisms, like bacteriophages, bacteria, yeasts, higher fungi, plants and animals. The pol and PR exonuclease domains are highly conserved in all these pols suggesting that these replicative DNA pols might have evolved possibly from a common ancestor gene and hence, could follow essentially the same mechanism of action. All the eukaryotic B-family pols possess the highly conserved -SLYPS- and -YGDTDS- motifs except the replicative ε pols. However, in the poxviral pols, the pentapeptide motif, -SLYPS- is slightly modified to –SLYPN-. However, the second motif is completely conserved in all. Another important deference between the poxviral pols and its host, i.e., human replicative pols is the presence of an HNH-type motif which is present only in the poxviral pols. Furthermore, the poxviral pols also differ in not possessing the regular ZBMs in their CTDs, which are invariably found in all three human replicative pols. A relatively thorough analyses of the poxvirus replication mechanism in mammalian cells could pave the way for the development of cost-effective antiviral drugs for this crucial enzyme to contain the spread of these deadly viruses in the future.

Compliance with ethical standards

Acknowledgments

The author wishes to thank Dr. N. Srinivasan, Former Professor, Department of Endocrinology, Post Graduate Institute of Basic Medical Sciences, University of Madras, Chennai, for useful suggestions on the manuscript.

Disclosure of conflict of interest

The author has declared that no competing interests exist.

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