

	1	*	*	*		*	*	55																																														
hum pol gamma aa seq	(1)	-MSRLLWRK	VAGATV	GP	GPVPA	PGRWVSSSV	ASD	PSDG	QRRR	QQ	QQQQ	QQQQQ																																										
Pan troglodytes (chimpanzee)	(1)	-MSRLLWRK	VAGATV	GP	GPVPA	PGRWVSSSV	ASD	PSDG	QRRR	QQ	QQQP	QQ--	<i>R3P-PEO</i>																																									
Macaca mulatta (rhesus monkey) pol gamma	(1)	-MSRLLWRK	LAGATV	VVP	GPVPA	PGRWVSSSV	ASD	PSDG	RRR	QQ	QLQP	QVP--	<i>G11D-Alpers</i>																																									
mus pol gamma	(1)	-MSRLLW	KKVAGAKV	AS	GPVPA	TARWVSSSV	LDPV	PSDG	--RPPS	Q	MP	----	<i>18P→S SNP</i>																																									
rat pol gamma	(1)	-MSRLLW	KKVAGAKV	AS	GPVPA	TGRWVSSSV	LDPV	PSDG	--QPQS	Q	MP	-----	<i>Q43R-idiopathic sporadic Parkinsons</i>																																									
Xenopus pol gamma	(1)	----	MNRL	LQK	GTSLVPSWRTRGCR	YRRC	S	YAPQLHAKPLEMETS	Q	RR	----	----	<i>49Q→E SNP</i>																																									
Drosophila pol gamma	(1)	-MQFH	LIRK	YASKVSREHYASSSVKIFRRV	KP	PQ	VNKP	PKK	PEN	VENG	----	----	<i>ΔGlu 43-55 -male infertility</i>																																									
scyeast pol gamma mip1	(1)	----	MTKLM	V	RSECMLRMVRRR	PLR	VQ	F	C	ARWFSTKKN	----	----																																										
S. pombe pol gamma	(1)	----	MFY	K	ACPSTLTCSKWIHSIIKTKKFLYCRHYS	S	KS	----	----	----	----	----																																										
Neurospora pol gamma	(1)	MLTPVRC	RTV	PNATV	ATAARVLRANLF	S	RY	P	R	QLGHLRWDSTIA	Q	VLERK	---																																									
Consensus	(1)	MSRLLWRK	VAG	V	GPVPA	RWVSSSV	PSDG			Q																																												
	56		*	*		*							110																																									
hum pol gamma aa seq	(55)	Q	PQPQ	QVLSSEGG	QLRHNPLDI	IQMLSRGLHE	QIFG	QGG	EM	FG	----	AAV	RRS	VE	<i>64S→L SNP</i>																																							
Pan troglodytes (chimpanzee)	(53)	-PQPQ	QVLSSEGG	QPRHNPLDI	IQMLSRGLHE	QIFG	QGG	EM	FG	----	AAV	RRS	VE	<i>Q68X - Alpers</i>																																								
Macaca mulatta (rhesus monkey) pol gamma	(53)	-----	SSEGG	QLRHNPLHI	IQMLSKGLHE	QIFG	QGG	EI	FG	----	AAV	RRS	VE	<i>L83P - Alpers</i>																																								
mus pol gamma	(46)	-----	SSENG	QLRLNPLLI	IQMLSRGLHE	QIFG	C	GG	EM	PD	----	AAV	QRS	VE																																								
rat pol gamma	(46)	-----	SSENG	QLRLNPLHI	IQMLSRGLHE	QIFG	C	GG	DV	PD	----	AAV	QRS	IE																																								
Xenopus pol gamma	(45)	-----	-----	MNPL	NIQMLSKGFHE	QIFR	GK	QV	QHAE	----	EDV	QRS	IT																																									
Drosophila pol gamma	(48)	-----	PTEYAEN	LVKV	QMSRNLH	ALF	P	Q	APRS	ISE	QQ-V	A	SAK	VYKD																																								
scyeast pol gamma mip1	(35)	-----	TAEAP	R	IN	VGL	QYL	G	ES	L	QR	V	F	C	SG	G	K	D	E	V	E	Q	S	D	K	L	M	E	L	S	K																							
S. pombe pol gamma	(36)	-----	FIDNAP	L	R	IN	V	G	V	Q	Y	L	S	P	A	I	Q	N	V	F	P	Q	N	T	Q	I	S	Q	----	L	H	L	D	L	A	K	F																	
Neurospora pol gamma	(53)	-----	LGVPSTAR	H	N	E	I	G	V	Q	L	S	E	H	I	Y	K	Q	L	F	P	R	C	N	T	D	P	P	A	P	---	E	L	I	E	L	A	K	D															
Consensus	(56)		SSE	G	Q	L	R	N	P	L	I	Q	M	L	S	R	G	L	H	E	Q	I	F	G	Q	G		P	E		AAV	R	S	E																				
	111	*												165																																								
hum pol gamma aa seq	(106)	HL	QKHGLWG	Q	AV	PLPD	VELR	LPPL	Y	GD	NLD	QHFRLLA	AQ	Q	S	LPYLEEA	NLL	Q	A																																			
Pan troglodytes (chimpanzee)	(103)	HL	QKHGLWG	Q	AV	PLPD	VELR	LPPL	Y	GD	NLD	QHFRLLA	AQ	Q	S	LPYLEEA	NLL	Q	A																																			
Macaca mulatta (rhesus monkey) pol gamma	(96)	HL	QKHGLWG	Q	AA	PLPD	VELR	LPPL	Y	GD	NLD	QHFRLLA	AQ	Q	S	LPYLEEA	N	S	L	L	Q	A																																
mus pol gamma	(89)	HL	QKHGLWG	Q	A	T	PLPD	VELR	LP	R	I	F	G	N	L	D	QHFRLLA	AQ	Q	S	LPYLEEA	A	S	L	L	E	A																											
rat pol gamma	(89)	HL	RKHGLWG	Q	P	T	PLPD	V	Q	L	R	I	F	G	N	L	D	QHFRLLA	AQ	Q	S	LPYLEEA	A	S	L	S	E	A																										
Xenopus pol gamma	(80)	HL	KNHELWG	Q	E	T	STVP	D	VEL	Q	L	P	K	M	Y	G	N	I	E	E	H	F	Q	I	L	AQ	Q	S	LPYLEEA	N	L	L	I	N	C																			
Drosophila pol gamma	(91)	E	LRRH	G	V	D	I	E	S	S	A	P	V	S	D	V	Q	L	K	L	P	P	L	R	G	A	N	I	E	E	H	F	H	N	I	A	K	E	V	Q	P	V	E	L	L	L	P	V	Q					
scyeast pol gamma mip1	(80)	S	L	K	D	H	G	L	W	G	K	K	T	L	I	T	D	P	I	S	F	P	L	P	L	Q	G	R	S	L	E	H	F	Q	K	I	G	R	F	N	S	E	P	Y	K	S	F	C	E	D	K	F	T	
S. pombe pol gamma	(79)	H	L	A	K	H	Q	L	L	N	K	E	T	I	K	L	S	F	N	F	R	L	P	L	Q	G	K	T	I	S	E	H	F	Y	N	I	G	L	E	F	A	E	P	H	L	S	K	A	I	K	F	S	K	I
Neurospora pol gamma	(97)	H	L	A	R	H	D	L	L	G	K	T	T	D	K	T	P	I	A	F	Q	L	P	A	L	V	G	D	T	L	L	E	H	F	H	K	L	G	V	D	A	A	E	P	F	L	T	H	A	K	Q	F	A	D
Consensus	(111)	HL	KHGLWG	Q	P	T	PLPD	VELR	LPPL	G	NLD	HFRLLA	AQ	Q	S	LPYLEEA	NLL	A																																				

166

220

hum pol gamma aa seq (161)
 Pan troglodytes (chimpanzee) (158)
 Macaca mulatta (rhesus monkey) pol gamma (151)
 mus pol gamma (144)
 rat pol gamma (144)
 Xenopus pol gamma (135)
 Drosophila pol gamma (146)
 scyeast pol gamma mip1 (135)
 S. pombe pol gamma (134)
 Neurospora pol gamma (152)
 Consensus (166)

* **EXOI**

(161) QLPPK-PPAWAWAEGWTRYGPEG-EAVPVAIPEERALVFDVEVCLAEGTCPTLAV
 (158) QLPPK-PPAWAWAEGWTRYGPEG-EAVPVAIPEERALVFDVEVCLAEGTCPTLAV
 (151) QLPPQ-PTGWAWAEGWTRYGPEG-EAVPVAIPEERALVFDVEVCLAEGTCPTLAV
 (144) QLPPQ-PTGWAWAEGWTRYGPEG-EAVPVAIPEERALVFDVEVCLAEGTCPTLAV
 (144) QLPPQ-PRKVVWAEWTRYGPEG-EAVPVAIPEERALVFDVEVCLAEGTCPTLAV
 (135) QLPAM-PQTWAWQSGWTRYTATG-EKELVDFPDKAMVFDVEVCLVTEGTCPTLAV
 (146) EQLPKRPKRWAFHTGWTAYDPEDEGATPVDPHLEKGLVFDVEVCLVTEGTCPTLAV
 (135) MVARP--AEWLRKPWVKYVFGM-APVEVAVPDELVFDVEVCLVTEGTCPTLAV
 (134) DTPVQ-PKTWKRQPGWTKYAKDG-SISCVPYFDSDCMVFDVEVCLVTEGTCPTLAV
 (152) HLPPK-PTSWVRRSGWTKYNRDG-TTENDVLPQGNMMCDFDEVMYKDNPIAVMAC
 (166) QLPP P WAWAEGWTRYGPEG EA PVAIPEERALVFDVEVCLAEG CPTLAV

193R→Q SNP

221

275

hum pol gamma aa seq (214)
 Pan troglodytes (chimpanzee) (211)
 Macaca mulatta (rhesus monkey) pol gamma (204)
 mus pol gamma (197)
 rat pol gamma (197)
 Xenopus pol gamma (188)
 Drosophila pol gamma (201)
 scyeast pol gamma mip1 (187)
 S. pombe pol gamma (187)
 Neurospora pol gamma (205)
 Consensus (221)

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(214) AISPRAWYSWCSQRLVEERYSWTSQSPADLIPLVPTGA--SPTQRDWQEQLV
 (211) AISPRAWYSWCSQRLVEERYSWTSQSPADLIPLVPTASA--SPTQRDWQEQLV
 (204) AISPRAWYSWCSRRRLVEERYSWTSQSPADLIPLVPTAG--ASPTQRDWQEQLV
 (197) AISPRAWYSWCSRRRLVEERYSWTSQSPADLIPLVGGSTSA--SSTKQDGEQLV
 (197) AISPRAWYSWCSRRRLVEERYSWTSQSPADLIPLVVSASA--SSTQDGEQLV
 (188) AASPQNWYSWCSRRRLVEERYSWTSQSPADLIPLVTSMNC--NYMTKNNWTERLV
 (201) AVSTKRWYSWVSSKLTKHRLSVEKLEPLDVTDSERPHYTPDELIPLGTSVSGPLV
 (187) ALSSTAWYLWCSPFICGGDDPAALIPLNLTN-----KQVI
 (187) AVSEDAWYCWLSPLWLGKSEN-DRQLIP-----S-----NPKGALF
 (205) AGTPEAWYAWLSPLWLGKSEN-DRQLIP-----S-----NPKGALF
 (221) AISPRAWYSWCS RLVVEERYSWTSQSPADLIPLV S T DWQEQLV

C224Y-Alpers, ...
 R227W-PEO, Alpers, ...
 R227P-multisys. Disor.
 R232H-Alpers & CMT
 R232G-Alpers & hepatocere.
 W235stop-multisystem
 disorder
 241P→L SNP
 L244P-Alpers
 T251I-PEO, Alpers, & infant
 hepatocerebral

276

330

hum pol gamma aa seq (267)
 Pan troglodytes (chimpanzee) (264)
 Macaca mulatta (rhesus monkey) pol gamma (256)
 mus pol gamma (250)
 rat pol gamma (250)
 Xenopus pol gamma (241)
 Drosophila pol gamma (256)
 scyeast pol gamma mip1 (223)
 S. pombe pol gamma (222)
 Neurospora pol gamma (242)
 Consensus (276)

* **EXOII** *

(267) VGHNVSFDRAHIREQYLIQGSRMRFLLDTMSMHMAISGLSSFORSLSWIAAKQGKHK
 (264) VGHNVSFDRAHIREQYLIQGSRMRFLLDTMSMHMAISGLSSFORSLSWIAAKQGKHK
 (256) VGHNVSFDRAHIREQYLIQGSRMRFLLDTMSMHMAISGLSSFORSLSWIAAKQGKHK
 (250) VGHNVSFDRAHIREQYLIQGSRMRFLLDTMSMHMAISGLSSFORSLSWIAAKQGKHK
 (250) VGHNVSFDRAHIREQYLIQGSRMRFLLDTMSMHMAISGLSSFORSLSWIAAKQGKHK
 (241) VGHNVSFDRAHIREQYLIQGSRMRFLLDTMSMHMAISGLSSFORSLSWIAAKQGKHK
 (256) VGHNVSFDRAHIREQYLIQGSRMRFLLDTMSMHMAISGLSSFORSLSWIAAKQGKHK
 (223) IGHNVAYDRAHIREQYLIQGSRMRFLLDTMSMHMAISGLSSFORSLSWIAAKQGKHK
 (222) VGHNVSFDRAHIREQYLIQGSRMRFLLDTMSMHMAISGLSSFORSLSWIAAKQGKHK
 (242) VGHNVSFDRAHIREQYLIQGSRMRFLLDTMSMHMAISGLSSFORSLSWIAAKQGKHK
 (276) VGHNVSFDRAHIREQYLIQGSRMRFLLDTMSMHMAISGLSSFORSLSWIAAKQGKHK

G268A-PEO
 H277C - Alpers
 L304R-PEO, Alpers, &
 ataxia-nueropathy
 S305R-Alpers
 Q308H-PEO
 R309L-PE
 R309H-Alpers
 W312R-PEO+/-,
 dysphagia/
 myopathy...

		331	*	*		*		385	
hum pol gamma aa seq	(322)	VQ	--PP	TKQ	GQKSQR	KARRG	--	PAISSWDWLDISSVNSLAEVHRLYVGGPPLEKE	
Pan troglodytes (chimpanzee)	(319)	VQ	--PS	TKQ	GQKSQR	KARRG	--	PAISSWDWLDISSVNSLAEVHRLYVGGPPLEKE	
Macaca mulatta (rhesus monkey) pol gamma	(311)	VQ	--GS	TKQ	GQKSQR	KARRG	--	PAISSWDWLDISSVNSLAEVHRLYVGGPPLEKE	
mus pol gamma	(305)	TQ	--QS	TKRGQKS	PRK	-ANG	--	PAISSWDWMDISSANNLADVHNLYVGGPPLEKE	
rat pol gamma	(305)	TQ	--HP	TKRGQKS	QKN	-ANG	--	PAISSWDWMDISSANNLADVHNLYVGGPRLAKE	
Xenopus pol gamma	(296)	GL	--QE	VKQHI	KKTR	SNFSG	--	SPISSWDWVNISSINNLADVHALYVGGPPLEKE	
Drosophila pol gamma	(305)	-----	KE	-----	-----	-----	-----	PAEEDLGWLEQSPLNLSLVEVHRLYCGGDTLSKE	
scyeast pol gamma mip1	(274)	-----	K	KEAEVESEV	HPEIS	IEDYDDP	WLNVS	ALNSLKDVAKFHCK-IDLDKT	
S. pombe pol gamma	(277)	SQ	STETSE	DDDDSS	SFDDDYQ	--NYLKQEP	WLAHSSVNSLKDVAKFHCN-ITLDKS		
Neurospora pol gamma	(297)	RE	KAHEHESAS	VELQ	EVLQGG	SLTAE	EEADLWVDKSSINSLRVAQFHLN-VKIDKD		
Consensus	(331)	Q	TK	GQKSQR	G	PAISSWDWLDISS	NSLADVH	LYVGGPPLEKE	

324P→S SNP
T326fsX387-Alpers
W347_L356del-Alpers

		386		*		*		440	
			*	*		*	EXOIII	**	*
hum pol gamma aa seq	(373)	PRELFVKG	TMKDIRENFQDLMQ	YCAQDVWATHEVFQQQLPLFLERC	PHPVTLAGM				
Pan troglodytes (chimpanzee)	(370)	PRELFVKG	TMKDIRENFQDLMQ	YCAQDVWATHEVFQQQLPLFLERC	PHPVTLAGM				
Macaca mulatta (rhesus monkey) pol gamma	(362)	PRELFVKG	TMKDIRENFQDLMQ	YCAQDVWATHEVFQQQLPLFLERC	PHPVTLAGM				
mus pol gamma	(355)	PRELFVKG	SMRDIRENFQDLMQ	YCARDVWATHEVFQQQLPLFLERC	PHPVTLAGM				
rat pol gamma	(355)	PRELFVKG	SMRDIRENFQDLMQ	YCARDVWATHEVFQQQLPLFLERC	PHPVTLAGM				
Xenopus pol gamma	(347)	ARELFVKG	SMSDIRTEFQELMRYCALDVQATHEVFQQQLPLFLERC	PHPVTLSGM					
Drosophila pol gamma	(340)	PRNIFVEG	TLEQVRQSFQSLITNYCASDVEATHRILRVLYPLIYAERF	PHPASLAGM					
scyeast pol gamma mip1	(321)	DRDFFAST	DKSTIIENFQKLVNYCATDV	TATSQVHDEIFVFLK	CPHPVSFAGL				
S. pombe pol gamma	(329)	KRDDFAS	LEKEPIIQKLNELITYCAHDTYSTHQVFKKVF	QFLVCPHPATFSAM					
Neurospora pol gamma	(351)	IRDVFA	ETDRNVIILNQLDILLTYCAADVQVTHQVYQVVF	ENFLGVC	PHPVSFAL				
Consensus	(386)	PRELFVKG	M DIRENFQDLM	YCA DVWATHEVFQQQLPLFLERC	PHPVTLAGM				

R374X -Alpers
G380D-PEO
392L→V SNP
L392V-muscle weakness,
optic atrophy
R417T - Alpers
C418R - Alpers
L424 (ct) del452stop-PEO
Alpers

		441		*		*		495	
			*	*	*		*	**	
hum pol gamma aa seq	(428)	LEMGSYLPVNQ	NWERYLAEAQ	GTYEELQREM	KKSLMDLANDACQLLSGERYKE				
Pan troglodytes (chimpanzee)	(425)	LEMGSYLPVNQ	NWERYLAEAQ	GTYEELQREM	KKSLMDLANDACQLLSGERYKD				
Macaca mulatta (rhesus monkey) pol gamma	(417)	LEMGSYLPVNQ	NWERYLAEAQ	GTYEELQREM	KKSLMDLANDACQLLSGERYKE				
mus pol gamma	(410)	LEMGSYLPVNQ	NWERYLAEAQ	GTYEELQREM	KKSLMDLANDACQLLSGERYKE				
rat pol gamma	(410)	LEMGSYLPVNQ	NWERYLAEAQ	GTYEELQREM	KKSLMDLANDACQLLSGERYKE				
Xenopus pol gamma	(402)	LEMGSYLPVNQ	NWERYLAEAQ	GTYEELQREM	KKSLMDLANDACQLLSGERYKE				
Drosophila pol gamma	(395)	LEMGSAYLPVNS	NWERYLAEAQ	GTYEELQREM	KKSLMDLANDACQLLSGERYKE				
scyeast pol gamma mip1	(376)	KLSKCI	LPTKLNDDNDYLNSS	ESLYQQSKVQIESKIVQIIKDIVLLKDKPDFYL					
S. pombe pol gamma	(384)	LSLGSVF	LPVNH-SWTRY	INGVEEQYQMIQLVDQKLSQYAEKAKDLINTKDTV					
Neurospora pol gamma	(406)	RHLASVI	LPVNK-TWDTY	IETAETYLQMLHGVQERLFTLMERTLDYKADPEKYL					
Consensus	(441)	LEMGSYLPVNQ	NWERYLAEAQ	GTYEELQREM	KKSLMDLANDACQLLSGERYKE				

L428P-Alpers,...
M430L-PEO
G431V-PEO
S433C-PEO, ataxia, ...
T452stop-PEO
L463F-PEO
A467T-PEO, SANDO,
MERRF, & Alpers...
N468D-PEO

	496	*	*	*	550																																												
hum pol gamma aa seq	(482)	DPWLWDLQEFKQKAKKVKKEP	ATASKLPIEGAG	GDPMDQEDLP	CSEE	<i>Q497H-Ataxia-Neuropathy</i>																																											
Pan troglodytes (chimpanzee)	(479)	DPWLWDLQEFKQKARKVKEP	ATASKLPIEGAG	GDPMDQEDLP	CSEE	<i>S511N-PEO</i>																																											
Macaca mulatta (rhesus monkey) pol gamma	(471)	DPWLWDLQEFKQKAKKVKKEP	ATASKLPIEGAG	GDPMDQEDLP	RSEE	<i>G517V- Ataxia-Neuropathy</i>																																											
mus pol gamma	(464)	DPWLWDLQEFKQKAKKVKKEP	ASASKLPIEGAG	GDPMDQEDLP	PPSEE																																												
rat pol gamma	(464)	DPWLWDLQEFKQKAKKVKKEP	ASASKLPIEGAG	GDPMDQEDLP	PPSEE																																												
Xenopus pol gamma	(456)	DPWLWDLQEFKQKAKKVKKEP	ASASKLPIEGAG	GDPMDQEDLP	PPSEE																																												
Drosophila pol gamma	(449)	NLWLDLQEFKQKAKKVKKEP	ASASKLPIEGAG	GDPMDQEDLP	PPSEE																																												
scyeast pol gamma mip1	(431)	KDPWLSQLDWTTKPLRLTKK	GVPAK	-----	-----																																												
S. pombe pol gamma	(438)	KDPWLRQLDWTTPCNLYR	KLKKATQE	-----	-----																																												
Neurospora pol gamma	(460)	SDPWLSQLDWSGQEIKMAKP	KKKG	-----	-----																																												
Consensus	(496)	DPWLWDLQEFKQKAKKVKK	A ASKLP	IEGAG	GDPMDQED GP SEE																																												
	551	*	**	*	*	*	605																																										
hum pol gamma aa seq	(537)	EEFQQDVMA	RACLQK	TKGTT	ELLPKR	PQHLPGH	PGWYR	KLCPR	-----	<i>546R→C SNP</i>																																							
Pan troglodytes (chimpanzee)	(534)	EEFQQDVMA	RACLQK	TKGTT	ELLPKR	PQHLPGH	PGWYR	KLCPR	-----	<i>K561M- dysmorphia, hypotonia, liver insufficiencies,</i>																																							
Macaca mulatta (rhesus monkey) pol gamma	(526)	EEFQQDVMA	RACLQK	TKGTT	ELLPKR	PQHLPGH	PGWYR	KLCPR	-----	<i>rat</i>																																							
mus pol gamma	(518)	EELQRSVT	AHNRLQ	LRSTT	DL	LLPKR	PQHLPGH	PGWYR	KLCPR	-----																																							
pol gamma (518)	(518)	EELQ	QNIMA	HTRLQ	QLKST	TDL	LLPKR	PQHLPGH	PGWYR	KLCPR	-----																																						
Xenopus pol gamma	(509)	EESRPSMG	KLYLED	LKLT	LP	LLPKR	NQHLPGH	PGWYR	KLCPR	-----																																							
Drosophila pol gamma	(482)	GNTPEERR	LQAKF	QH	YDQQ	ALLP	ARRPL	LPGY	ELWYR	KLCPR	KRKPPAKREDEILED																																						
scyeast pol gamma mip1	(456)	-----	-----	-----	-----	C	KLPG	FEWYR	QLF	FSK	-----																																						
S. pombe pol gamma	(463)	-----	VP	-----	-----	-----	V	VEK	WYK	KAY	CKT	-----																																					
Neurospora pol gamma	(484)	-----	-----	-----	-----	D	VER	PALN	QK	LPG	YEQWY	KDLF	VKVPKEL	SGLDEPD																																			
Consensus	(551)	EE Q	A	LQ	L	TT	LLPKR	PQHLPGH	PGWYR	KLCPR	L																																						
	606	*	*	*	*	*	*	660																																									
hum pol gamma aa seq	(581)	DDPAW	T	PGPSLL	SLQMR	VT	PKL	MAL	T	WDGF	P	LHYS	ER	H	GW	G	YL	V	P	G	R	R	D	N	L	A																							
Pan troglodytes (chimpanzee)	(578)	DDPAW	T	PGPSLL	SLQMR	VT	PKL	MAL	T	WDGF	P	LHYS	ER	H	GW	G	YL	V	P	G	R	R	D	N	L	A																							
Macaca mulatta (rhesus monkey) pol gamma	(570)	DDPAW	T	PGPSLL	SLQMR	VT	PKL	MAL	T	WDGF	P	LHYS	ER	H	GW	G	YL	V	P	G	R	R	D	N	L	A																							
mus pol gamma	(562)	DDPAW	A	PGPSLL	SLQMR	VT	PKL	MAL	T	WDGF	P	LHYS	D	S	H	GW	G	YL	V	P	G	R	R	D	N	L	T																						
rat pol gamma	(562)	DDPAW	T	PGPSLL	SLQMR	VT	PKL	MAL	T	WDGF	P	LHYS	D	S	H	GW	G	YL	V	P	G	R	R	D	N	L	T																						
Xenopus pol gamma	(553)	EDPD	W	LP	GLI	SLQMR	L	T	PKL	M	R	L	T	WDG	Y	P	L	H	Y	S	E	K	H	G	W	G	Y	L	V	P	G	R	K	N	N	K	L												
Drosophila pol gamma	(537)	DEEP	W	SP	GA	EI	S	T	G	M	Q	I	A	P	K	L	S	L	S	C	W	E	G	Y	P	L	H	Y	S	E	R	E	Q	G	W	G	F	L	V	P	F	R	S	D	S				
scyeast pol gamma mip1	(474)	-----	D	T	V	E	P	K	I	T	I	K	S	R	I	I	P	I	L	F	K	L	S	W	E	N	S	E	P	V	I	W	S	K	E	S	G	W	C	F	N	V	P	H	E	Q	V	E	T
S. pombe pol gamma	(478)	-----	E	K	R	A	V	I	T	A	K	S	R	L	A	P	I	L	L	R	L	K	W	K	K	H	P	L	A	W	S	D	T	Y	G	W	V	F	S	V	E	R	T	S	K	D			
Neurospora pol gamma	(520)	KEQ	E	N	R	K	A	R	H	E	F	I	N	L	T	V	R	S	R	I	A	P	L	L	K	L	S	W	E	G	Y	P	L	F	W	S	D	Q	F	G	W	T	F	Q	V	P	R	E	K
Consensus	(606)	DDPAW		PGPSLL	SLQMR	VT	PKL	MAL	T	WDGF	P	LHYS			HGW	G	YL	V	P	G	R	R	D	N	L	A																							

		826		*		**	*		880	
hum pol gamma aa seq	(795)	NKMISFWRNAHKRISSQMVVWLP	PRSA	LPRAVIR	RHPDYDE	---	EGLYGAILPQVV			R807P-PEO
Pan troglodytes (chimpanzee)	(792)	NKMISFWRNAHKRISSQMVVWLP	PRSA	LPRAVIR	RHPDYDE	---	EGLYGAILPQVV			R807C- SANDO
Macaca mulatta (rhesus monkey) pol gamma	(784)	NKMISFWRNAHKRISSQMVVWLP	PRSA	LPRAVIR	RHPDYDE	---	EGLYGAILPQVV			c.2480+1-Alpers
mus pol gamma	(773)	NKMISFWRNAHKRISSQMVVWLP	PRSA	LPRAVIR	RHPDYDE	---	EGHYGAILPQVV			IVS15-9 c.2485del-
rat pol gamma	(772)	NKMISFWRNAHKRISSQMVVWLP	PRSA	LPRAVIR	RHPDYDE	---	ESHYGAILPQVV			Alpers
Xenopus pol gamma	(765)	NKMISFWRNAHKRISSQMVVW	MKKNEL	HR	TITRDE	EFDE	---	ENKYGAILAQVVS		Y831C-PEO &
Drosophila pol gamma	(715)	ARMMSYWRNRDRIMGQLV	WLD	SQQL	NEFTG	--	EKCQ---	PIAYGAI	CPQVVA	Parkinsonism
scyeast pol gamma mip1	(595)	NSSGSYWMSARERIQS	QFV	VP	PSCKFPNEF	QSLSAKSS	LNNEKTNDLAI	I	PKIVP	
S. pombe pol gamma	(593)	SASCYWSSARDRIR	SQMVV	DKDAEL	GVPSSVD	--	G-----	FGI	ILPCIIP	
Neurospora pol gamma	(645)	NASCYWISARERIKN	QMVV	YEDQL	PPSQRFV	NKDADSN	---	TPIG	GFVLPQVIP	
Consensus	(826)	NKMISFWRNAHKRISSQMVVWLP	PRSA	LPRAVIR	RHP	DE		E	YGAILPQVV	
		881						<u>PolA</u>	935	
hum pol gamma aa seq	(847)	AGTITRRAVEPTWLTASNAR	PDRV	GSELKAMVQAPP	PGYTLV	GADVDSQELWIAAV				G848S-PEO & Alpers, &
Pan troglodytes (chimpanzee)	(844)	AGTITRRAVEPTWLTASNAR	PDRV	GSELKAMVQAPP	PGYTLV	GADVDSQELWIAAV				MELAS
Macaca mulatta (rhesus monkey) pol gamma	(836)	AGTITRRAVEPTWLTASNAR	PDRV	GSELKAMVQAPP	PGYTLV	GADVDSQELWIAAV				T849H-Alpers
mus pol gamma	(825)	AGTITRRAVEPTWLTASNAR	PDRV	GSELKAMVQAPP	PGYTLV	GADVDSQELWIAAV				T851A- Alpers
rat pol gamma	(824)	AGTITRRAVEPTWLTASNAR	PDRV	GSELKAMVQAPP	PGYTLV	GADVDSQELWIAAV				R852C-Alpers
Xenopus pol gamma	(817)	AGTITRRAVEPTWLTASNAR	ADRV	GSELKAMVQAPP	PGYHLI	GADVDSQELWIAAI				R853Q-Myocerebrohepat.
Drosophila pol gamma	(765)	CRTLTRRAMEPTWMTASN	SRPDR	LGSELRS	MVQAPP	PGYRLV	GADVDSQELWIASV			R853W-PEO w/ptosis &
scyeast pol gamma mip1	(650)	MGTITTRAVENAWLTASN	KANR	IGSELK	TQVKAPP	PGYCFV	GADVDSQELWIASL			Parkinsonism
S. pombe pol gamma	(638)	MGTITTRAVENTWLTASN	SKKNR	LGSELKAM	IRAP	DGYTFV	GADVDSQELWIVAL			V855A-muscle weakness
Neurospora pol gamma	(697)	MGTITTRAVEERTWLTASN	AKKNR	VGSELKAM	VRAPP	PGYVVF	GADVDSQELWIASV			A862T-Ataxia & PEO
Consensus	(881)	AGTITRRAVEPTWLTASNAR	PDRV	GSELKAMVQAPP	PGYLV	GADVDSQELWIAAV				N864S-PEO
		936						<u>PolB</u>	990	
hum pol gamma aa seq	(902)	LGDAHFAGMHGCTAF	GWM	LQGRKSRG	TDLH	SKTATTVGISREHAKIFNYGRIY				T914P-PEO, Alpers...
Pan troglodytes (chimpanzee)	(899)	LGDAHFAGMHGCTAF	GWM	LQGRKSRG	TDLH	SKTATTVGISREHAKIFNYGRIY				W918R - PEO
Macaca mulatta (rhesus monkey) pol gamma	(891)	LGDAHFAGMHGCTAF	GWM	LQGRKSRG	TDLH	SKTATTVGISREHAKVFNYGRIY				G923D-PEO
mus pol gamma	(880)	LGDAHFAGMHGCTAF	GWM	LQGRKSRG	TDLH	SKTAAATVGISREHAKIFNYGRIY				H932Y-PEO, & SANDO
rat pol gamma	(879)	LGDAHFAGMHGCTAF	GWM	LQGRKSRG	TDLH	SKTAAATVGISREHAKVFNYGRIY				R943C-Myocerebrohepat
Xenopus pol gamma	(872)	LGEAHFAGIHGCTAF	GWM	LQGRKSRG	TDLH	SKTAAATVGISREHAKVFNYGRIY				R943H-PEO
Drosophila pol gamma	(820)	LGDAYACGEHGATPLG	WM	LSGSKNSG	SDMHS	ITAKAVGISRDHAKVINYARTY				R953C-PEO
scyeast pol gamma mip1	(705)	VGDSIFN-VHGGTA	IGW	MLEG	TKNEG	TDLH	TKTAAQILGCSRNEAKIFNYGRIY			Y955C-PEO, &
S. pombe pol gamma	(693)	MGDSQFR-LHGATA	LGW	MLEG	TKNEG	TDLH	SKTAAAILGVS	RD	SAKVFNYGR	Parkinsonism...
Neurospora pol gamma	(752)	VGDAIFK-LHGNA	IGF	MTLE	GTKSQ	TDLH	SRTA	SILGITR	ND	AKVFNYGRIY
Consensus	(936)	LGDAHFAGMHGCTAF	GWM	LQGRKSRG	TDLH	SKTATTVGISREHAKVFNYGRIY				

		991		1045	
			* * **		
hum pol gamma aa seq	(957)	AGQPFAERLLMQFNHRLTQOEAAEKAQQMYAATKGLRWYRLSDEGEWLVRELNLP			A957S-PEO
Pan troglodytes (chimpanzee)	(954)	AGQPFAERLLMQFNHRLTQOEAAEKAQQMYAATKGLRWYRLSDEGEWLVRELNLP			A957P-Alpers
Macaca mulatta (rhesus monkey) pol gamma	(946)	AGQPFAERLLMQFNHRLTQOEAAEKAQQMYAATKGLRWYRLSDEGEWLVRELHLP			F961S - adPEO
mus pol gamma	(935)	AGQSFAERLLMQFNHRLTROEAAEKAQQMYAVTKGLRWYRLSADGEWLVKQINLP			R964C-Mitoch. tox.to
rat pol gamma	(934)	AGQSFAERLLMQFNHRLSRQEAAEKAQQMYAVTKGLRWYRLSDDGEWLVKQINVP			NRTI'S
Xenopus pol gamma	(927)	AGQPFAERLLMQFNHRLTQEQAEEKAQQMYAVTKGIRRYILSKEGEWLVEELGIS			L965stop-PEO
Drosophila pol gamma	(875)	AGQLFAETLLRQFNPTFSASEAKAKAMKMFSTKGRVYRLRELFHDELEDRAYS			L966R-Alpers
scyeast pol gamma mip1	(759)	AGAKFASQLLKRFPNPSLTDEETKKIANKLYENTKGRKTK-RSK-----			
S. pombe pol gamma	(747)	AGLKHTTLLMQMNPDKTAEAKELAKKLYASTKGVKSKMSKRLQEMGLPKLT--			
Neurospora pol gamma	(806)	AGLKFASQLLKRFPNPSLTAEFTTAIAATKLYDATKGAKTNRKS-----			
Consensus	(991)	AGQ FAERLLMQFNHRLT QEAAEKAQQMYA TKGLR YRLS EGEWLV L P			
		1046	*	*	*
hum pol gamma aa seq	(1012)	VDRTEGGWISLQDLRKVQRE TARKSQWKK-WEVVAERAWKGGTESEMFNKLESIA			W1020stop-Alpers
Pan troglodytes (chimpanzee)	(1009)	VDRTEGGWISLQDLRKVQRE TARKSQWKK-WEVVAERAWKGGTESEMFNKLESIA			R1047Q-PEO
Macaca mulatta (rhesus monkey) pol gamma	(1001)	VDRTEGGWISLQDLRKVQRE AARKSHRKK-WEVIAERAWKGGTESEMFNKLESIA			R1047W-Alpers & PEO
mus pol gamma	(990)	VDRTEGDWVSLQDLRMIRREASRKS RWKK-WEVASERAWTGGTESEMFNKLESIA			G1051R-PEO, & SANDO
rat pol gamma	(989)	VDRTEGDWVSLQDLRIRREASRKS RWKK-WEVVTERAWTGGTESEMFNKLESIA			
Xenopus pol gamma	(982)	VERGEENSVNLQDLRKIQKDATKRSRRK--WNLVSRRIWTTGGTESQMFNKLETIA			
Drosophila pol gamma	(930)	SYEASRLAIQ-----RNRTLAEV FHRPNWQGGTESAMFNRLLEEIA			
scyeast pol gamma mip1	(800)	-----LFKKFWYGGSESILFNKLESIA			
S. pombe pol gamma	(800)	-----FWSQGTESFVFNKLEAMA			
Neurospora pol gamma	(848)	-----LYKRPFWRGGTESFVFNMLEEFA			
Consensus	(1046)	VDRTE GW SLQDLRK RE RKS KK WEV ERAW GGTESEMFNKLESIA			
		1101	* *	**	***
hum pol gamma aa seq	(1066)	TSDIPRTPVLGCCI SRAL EPSA---VQEEFMTSRVNWVQSSAVDY LHLMLVAMK			G1076V-PEO
Pan troglodytes (chimpanzee)	(1063)	TSDIPRTPVLGCCI SRAL EPSA---VQEEFMTSRVNWVQSSAVDY LHLMLVAMK			I1079L-adPEO
Macaca mulatta (rhesus monkey) pol gamma	(1055)	TSDIPRTPVLGCRISRAL EPSA---VQGEFMTSRVNWVQSSAVDY LHLMLVAMK			S1095R-adPEO
mus pol gamma	(1044)	MSDTPRTPVLGCCI SRAL EPSV---VQGEFITSRVNWVQSSAVDY LHLMLVAMK			R1096C-PEO & Alpers
rat pol gamma	(1043)	MSDTPRTPVLGCCI SRAL EPSV---VQGEFITSRVNWVQSSAVDY LHLMLVAMK			R1096H-Alpers
Xenopus pol gamma	(1035)	MSPSPKTPVLGCRISRAL EPTA---VKGEFITSRVNWVQSSAVDY LHLMLVAMK			S1104C-PEO
Drosophila pol gamma	(970)	TGSQPRTPFLGGRLSRAL EADTGPEQEQRF LPTRINWVQSSGAVDF LHLMLVSMR			A1105T-PEO
scyeast pol gamma mip1	(822)	EQETPKTPVLGCGITYSIMKKN--LRANSELP SRINWAIQSSGVDYLHLLCCSME			V1106I-PEO
S. pombe pol gamma	(818)	QLPSPRTPVLDAGIQQALSSKN--LSKNSEMTSRVNWAIQSSAVDY LHLMLVSMN			
Neurospora pol gamma	(871)	EQERPRTPVLGAGITEALMSRWVS--KGGFLTSRINWAIQSSGVDYLHLIIAM			
Consensus	(1101)	SD PRTPVLGCI SRAL EPS VQGEFMTSRVNWVQSSAVDY LHLMLVAMK			

		<u>Pol C</u>												
		1156	*	*	**	*	*	*	*	*	*	1210		
hum pol gamma aa seq	(1118)	WLFEEFAIDGRFCISIHDEVRYLVREEDRYRAALALQITNLLTRCMFAYKLGND												
Pan troglodytes (chimpanzee)	(1115)	WLFEEFAIDGRFCISIHDEVRYLVREEDRYRAALALQITNLLTRCMFAYKLGND												
Macaca mulatta (rhesus monkey) pol gamma	(1107)	WLFEEFAIDGRFCISIHDEVRYLVREEDRYRAALALQITNLLTRCMFAYKLGND												
mus pol gamma	(1096)	WLFEEFAIDGRFCISIHDEVRYLVREEDRYRAALALQITNLLTRCMFAYKLGND												
rat pol gamma	(1095)	WLFEEFAIDGRFCISIHDEVRYLVREEDRYRAALALQITNLLTRCMFAYKLGND												
Xenopus pol gamma	(1087)	WLFEAYDIDGRFCISIHDEVRYLVHSDRYRAALALQITNLLTRCMFASRLGIQD												
Drosophila pol gamma	(1025)	WLMG---SHVRFCLSFHDELRYLVKEELSPKAALAMHITNLMTRSFVSRIGLQD												
scyeast pol gamma mip1	(875)	YIIKKYNLEARLCISIHDEIRFLVSEKDKYRAAMALQISNIWTRAMFCQQMGINE												
S. pombe pol gamma	(871)	HLIKKYYLEARLSLTVHDEVRYLVSSDKDKYRVAFALQVANLWTRAFFCQRLGINE												
Neurospora pol gamma	(924)	YLTRRFNLACRLAITVHDEIRYLAEEFDPKYRVAMALQIANLWTRVMFAQQVGIQD												
Consensus	(1156)	WLFEEFAIDGRFCISIHDEVRYLVREEDRYRAALALQITNLLTRCMFAYKLGND												
		1211	*	*	*	*	*	*	*	*	*	1265		
hum pol gamma aa seq	(1173)	LPQSVAFFSAVDIDRCLRKEVTMDCKTPSNPTGMERRYGIPOGEALDIYQIIELT												
Pan troglodytes (chimpanzee)	(1170)	LPQSVAFFSAVDIDRCLRKEVTMDCKTPSNPTGMERRYGIPOGEALDIYQIIELT												
Macaca mulatta (rhesus monkey) pol gamma	(1162)	LPQSVAFFSAVDIDRCLRKEVTMDCKTPSNPTGMERRYGIPOGEALDIYQIIELT												
mus pol gamma	(1151)	LPQSVAFFSAVDIDQCLRKEVTMDCKTPSNPTGMERRYGIPOGEALDIYQIIELT												
rat pol gamma	(1150)	LPQSVAFFSAVDIDQCLRKEVTMDCKTPSNPTGMERKYGIPQGEALDIYQIIELT												
Xenopus pol gamma	(1142)	VPQSVAFFSAVDIDKCLRKEVTMDCKTPSNPTGMERKYGIPQGEALDIYQIIELT												
Drosophila pol gamma	(1077)	LPMSVAFFSSVEVDTVLRKECTMDCKTPSNPTGMERKYGIPQGEALDIYQIIELT												
scyeast pol gamma mip1	(930)	LPQNCVAFFSQVDIDSVIRKEVNMDCITPSNPTGMERKYGIPQGEALDIYQIIELT												
S. pombe pol gamma	(926)	LPQSVAFFSSVDIDHVLRLKDVKMDCVTPSNKVPIPPGEELTIESVLEKLEQSGQS												
Neurospora pol gamma	(979)	LPQSCVAFFSAVDIDHVLRLKEVDMDCIITPSNPTGMERKYGIPQGEALDIYQIIELT												
Consensus	(1211)	LPQSVAFFSAVDID CLRKEVTMDCKTPSNPTGMERRYGIPOGEALDIYQIIELT												
		1266	*	*	1320									
hum pol gamma aa seq	(1228)	KGSLEKRSQPGP												
Pan troglodytes (chimpanzee)	(1225)	KGSLEKRSQPGP												
Macaca mulatta (rhesus monkey) pol gamma	(1217)	KGSLEKRSQPGP												
mus pol gamma	(1206)	KGSLEKRSQPGP												
rat pol gamma	(1205)	KGSLEKRSQPGP												
Xenopus pol gamma	(1197)	KGVL												
Drosophila pol gamma	(1132)	GGNDVSQWDWIKKS												
scyeast pol gamma mip1	(985)	PNLDIDSKVSYAYNYREPVFEEYNKSYTPEFLKYFLAMQVQSDKRDVNRLEDEY												
S. pombe pol gamma	(981)	LEPLEQIQCFVDVKATTSAEITEEDKKNIAYLKAQAFY												
Neurospora pol gamma	(1034)	DSIVPQSQYAPRLENIPYTPRPVPMQRLRERAEAGDHQAF LRFIRAQITNSDEEL												
Consensus	(1266)	KGSLEKRSQPGP												

R1128H-Micorcephaly
R1138C-PEO
1142R→W SNP
1143E→G SNP, PEO, ...
1146R→C SNP
3482+2TX21splice-Alpers
M1163R-Alpers
F1164I-PEO

L1173fs stop- Alpers
S1176L-PEO
D1184N-PEO
R1187W-?
K1191N-Alpers
K1191R-Myocerebrohep.
D1196N-Myopathy
G1205A-hearing loss, failure to thrive, & ETC complex defic.
Y1210fs-1216stop-Alpers

1230S→F SNP
1236Q→H SNP, PEO
Alpers

		1321		1375
	hum pol gamma aa seq	(1240)	-----	
	Pan troglodytes (chimpanzee)	(1237)	-----	
Macaca mulatta (rhesus monkey)	pol gamma	(1229)	-----	
	mus pol gamma	(1218)	-----	
	rat pol gamma	(1217)	-----	
	Xenopus pol gamma	(1201)	-----	
	Drosophila pol gamma	(1146)	-----	
	scyeast pol gamma mip1	(1040)	LRECTSKEYARDGNTAEYSLLDYIKDVEK GKRTKVRIMGSNFLDGT KNAKADQRI	
	S. pombe pol gamma	(1019)	-----	
	Neurospora pol gamma	(1089)	KRIIAETRYSDPYGAFSLASNGRVSGNPHQRHAAVHASTKTAAAPSKPSIASRFD	
	Consensus	(1321)		
		1376		1430
	hum pol gamma aa seq	(1240)	-----	
	Pan troglodytes (chimpanzee)	(1237)	-----	
Macaca mulatta (rhesus monkey)	pol gamma	(1229)	-----	
	mus pol gamma	(1218)	-----	
	rat pol gamma	(1217)	-----	
	Xenopus pol gamma	(1201)	-----	
	Drosophila pol gamma	(1146)	-----	
	scyeast pol gamma mip1	(1095)	RLPVNMPDYPTLHKIANDSAIPEKQLLENRRK KENRIDDENKKK LTRKKNTTPME	
	S. pombe pol gamma	(1019)	-----	
	Neurospora pol gamma	(1144)	SVSQASRIKSVAAGSDEPTIRATKAQ GKAMAKASG TKLAASTKDTV LNVTIKKKV	
	Consensus	(1376)		
		1431		1485
	hum pol gamma aa seq	(1240)	-----	
	Pan troglodytes (chimpanzee)	(1237)	-----	
Macaca mulatta (rhesus monkey)	pol gamma	(1229)	-----	
	mus pol gamma	(1218)	-----	
	rat pol gamma	(1217)	-----	
	Xenopus pol gamma	(1201)	-----	
	Drosophila pol gamma	(1146)	-----	
	scyeast pol gamma mip1	(1150)	RKYKRVYGGRKAF EAFYECANKPLDY TLETEKQFFNIPIDGV IDDLNDKSNYKK	
	S. pombe pol gamma	(1019)	-----	
	Neurospora pol gamma	(1199)	AAPEMAAVPSTSS ESKSKASATTTSTTTTENAT ASPSSSNVDAKKTTSKTKPTHK	
	Consensus	(1431)		

	1486	1537
hum pol gamma aa seq (1240)	-----	-----
Pan troglodytes (chimpanzee) (1237)	-----	-----
Macaca mulatta (rhesus monkey) pol gamma (1229)	-----	-----
mus pol gamma (1218)	-----	-----
rat pol gamma (1217)	-----	-----
Xenopus pol gamma (1201)	-----	-----
Drosophila pol gamma (1146)	-----	-----
scyeast pol gamma mip1 (1205)	KPSQARTASSSPIRKTAHAVHSHKLPARKSSTTNRNLVELERDITISREY--	
S. pombe pol gamma (1019)	-----	-----
Neurospora pol gamma (1254)	KETEGETFPFSLDDPVIAARLEAVSKTSPGTRASVAAKLDALASFCHASCCGC	
Consensus (1486)		