

**Supplementary Table 1 : causal mutations identified in index cases.**

**(a) Familial cases: mutations identified in the affected parents**

Definitively pathogenic mutations

Case #	Gene	Exon/ Intron	Nucleotide change	Effect on Protein	Mutation type	Reference
3	<i>PKD1</i>	1 to 5	c.1-?_1201+?del ( <i>PKD1</i> )		large rearrangement	This study
13	<i>PKD1</i>	5	c.1010_1013dup		frameshift	This study
29	<i>PKD1</i>	11	c.2582G>A	p.Trp861*	nonsense	<sup>1</sup>
17	<i>PKD1</i>	11	c.2833_2834del		frameshift	<sup>1</sup>
20	<i>PKD1</i>	14	c.3202del		frameshift	This study
1	<i>PKD1</i>	15	c.4804del		frameshift	This study
22	<i>PKD1</i>	15	c.5764C>T	p.Gln1922*	nonsense	<sup>2</sup>
31	<i>PKD1</i>	15	c.5873G>A	p.Trp1958*	nonsense	This study
7	<i>PKD1</i>	15	c.6472C>T	p.Gln2158*	nonsense	<sup>3</sup>
35	<i>PKD1</i>	15	c.6472C>T	p.Gln2158*	nonsense	<sup>3</sup>
18	<i>PKD1</i>	15	c.6548_6551del	p.Thr2183Serfs*28	frameshift	This study
39	<i>PKD1</i>	15	c.6727_6730del	p.Gln2243Alafs*6	frameshift	<sup>1</sup>
34	<i>PKD1</i>	25	c.8998del	p.Arg3000Alafs*74	frameshift	This study
16	<i>PKD1</i>	25	c.9089_9096del	p.Leu3030Profs*36	frameshift	This study
42	<i>PKD1</i>	33	c.10232G>A	p.Trp3411*	nonsense	This study
40	<i>PKD1</i>	33	c.10343del	p.Pro3448Glnfs*25	frameshift	<sup>1</sup>
41	<i>PKD1</i>	33	c.10343del	p.Pro3448Glnfs*25	frameshift	<sup>1</sup>
28	<i>PKD1</i>	41	c.11538-2A>G		splicing	<sup>1</sup>
27	<i>PKD1</i>	42	c.11713-2A>G		splicing	<sup>1</sup>
38	<i>PKD1</i>	42	c.11614G>T	p.Glu3872*	nonsense	<sup>3</sup>
32	<i>PKD1</i>	43	c.11884C>T	p.Gln3962*	nonsense	This study
26	<i>PKD1</i>	43	c.12003+1G>A		splicing	<sup>1</sup>
25	<i>PKD1</i>	45	c.12440dup	p.Glu4148Glyfs*9	frameshift	This study
14	<i>PKD1</i>	46	c.12503dup	p.Ser4169Leufs*41	frameshift	This study

Highly likely pathogenic missense mutations

Case #	Gene	Nucleotide change	Effect on protein	Position on PC-1 orthologs	Exon	Grantham Distance	Align GVGD		Polyphen		SIFT		Mutation Taster			Remarks	Reference
							Class	Prediction <sup>(a)</sup>	Score	Prediction	Score	Prediction	Probability				
37	<i>PKD1</i>	c.689G>C	p.Cys230Ser	Invariant	5	112	C0	B	0.99	Deleterious	0	Disease causing	0.995	Highly Likely pathogenic <sup>(b)</sup>	<sup>2</sup>		
6	<i>PKD1</i>	c.2180T>C	p.Leu727Pro	Invariant	11	98	C65	PD	1	Deleterious	0.01	Disease causing	1	Highly Likely pathogenic <sup>(b)</sup>	<sup>2</sup>		
8	<i>PKD1</i>	c.7108T>A	p.Cys2370Ser	Invariant	17	112	C0	PD	1	Deleterious	0	Disease causing	1	Highly Likely pathogenic <sup>(b)</sup>	<sup>2</sup>		
36	<i>PKD1</i>	c.7115C>G	p.Ser2372Cys	Invariant	17	112	C65	PD	1	Deleterious	0	Disease causing	1	Likely pathogenic <sup>(b)</sup>	<sup>1</sup>		

(a) PD : Probably damaging, PoD : Possibly damaging, B : Benign; (b) pkdb.mayo.edu/

## Likely pathogenic missense mutations

Case #	Gene	Nucleotide change	Effect on protein	Position on PC-1 orthologs	Exon	Grantham Distance	Align GVGD		Polyphen		SIFT		Mutation Taster		Remarks	Reference
							Class	Prediction <sup>(a)</sup>	Score	Prediction	Score	Prediction	Probability			
21	<i>PKD1</i>	c.5517G>T	p.Trp1839Cys	Invariant	15	215	C0	PD	1	Deleterious	0	Disease causing	1		This study	
19	<i>PKD1</i>	c.7978G>T	p.Asp2660Tyr	Invariant	21	160	C15	PD	1	Deleterious	0.01	Disease causing	1		This study	
24	<i>PKD1</i>	c.8497C>T	p.Pro2833Ser	Invariant	23	74	C65	PD	1	Deleterious	0	Disease causing	1		This study	
23	<i>PKD1</i>	c.9562A>G	p.Asn3188Asp	Invariant	27	23	C15	PD	1	Deleterious	0	Disease causing	1		This study	
12	<i>PKD1</i>	c.9563A>T	p.Asn3188Ile	Invariant	27	149	C65	PD	1	Deleterious	0	Disease causing	1		This study	
11	<i>PKD1</i>	c.11969T>G	p.Leu3990Arg	Invariant	43	102	C65	PD	1	Deleterious	0.01	Disease causing	0.966		This study	
2	<i>PKD2</i>	c.964C>G	p.Arg322Gly		4	125	C65	PD	0.999	Deleterious	0	Disease causing	1	Highly Likely pathogenic <sup>(b)</sup>	<sup>4</sup>	
15	<i>PKD2</i>	c.974G>C	p.Arg325Pro		4	103	C35	PD	0.993	Deleterious	0.02	Disease causing	0.998		This study	

(a) PD : Probably damaging, PoD : Possibly damaging, B : Benign; (b) pkdb.mayo.edu/

## Likely pathogenic other mutations

Case #	Gene	Exon/Intron	Nucleotide change	Effect on Protein	Mutation type	Position on PC-1 orthologs	Reference
33	<i>PKD1</i>	21	c.8017-3C>G		Splicing <sup>(c)</sup>		This study
10	<i>PKD1</i>	27	c.9568G>A		Splicing <sup>(d)</sup>		This study
30	<i>PKD1</i>	41	c.11451_11453dup	p.Gly3818dup	indel in frame		This study

## (b) sporadic cases : *de novo* mutations

Case #	Gene	Nucleotide change	Effect on protein	Position on PC-1 orthologs	Exon	Grantham Distance	Align GVGD		Polyphen		SIFT		Mutation Taster		Remarks	Reference
							Class	Prediction <sup>(a)</sup>	Score	Prediction	Score	Prediction	Probability			
4	<i>PKD1</i>	c.2534T>C	p.Leu845Ser	Invariant	11	145	C65	PD	1	Deleterious	0.01	Disease causing	0.997	Highly Likely pathogenic <sup>(b)</sup>	<sup>5</sup>	
9	<i>PKD1</i>	c.8536A>C	p.Thr2846Pro	Invariant	23	38	C35	PD	1	Deleterious	0	Disease causing	1		This study	

(a) PD : Probably damaging, PoD : Possibly damaging, B : Benign; (b) pkdb.mayo.edu/ (c): acceptor splice site of intron 21 is shifted 2 bp upstream with a score of 78.3 (SpliceSiteFinder-like); (d) score of donor splice site of intron 27 is greatly reduced (from 79.6 to zero according to SpliceSiteFinder-like)

**Supplementary Table 2 : Missense *PKD1* variations identified in families, inherited from an unaffected parent, in addition to the causal mutation**

Case #	Nucleotide change	Effect on protein	Position on PC-1 orthologs	Exon	Grantham Distance	Class	Align GVGD		Polyphen		SIFT		Mutation Taster			Remarks	Reference
									Prediction <sup>(a)</sup>	Score	Prediction	Score	Prediction	Probability			
18	c.3994G>A	p.Asp1332Asn	Highly conserved	15	23	C15	PD	0.985	Deleterious	0	Disease causing	1	LikelyNeutral <sup>(d)</sup>		6		
39	c.4031C>T	p.Thr1344Met <sup>(b)</sup>	Highly conserved	15	81	C0	PD	0.964	Deleterious	0.01	Polymorphism	1	rs185685883 (MAF 0.002/4)	This study			
14	c.4831G>A	p.Val1611Ile	Invariant	15	29	C25	PD	1	Tolerated	0.17	Disease causing	1				This study	
21	c.5830G>A	p.Gly1944Arg	Invariant	15	125	C0	PD	1	Deleterious	0	Disease causing	1	rs200001471 (MAF 0.01%)	This study			
23	c.6173A>G	p.Gln2058Arg	Highly conserved	15	43	C0	PD	0.999	Deleterious	0	Disease causing	1				This study	
13	c.8129C>A	p.Thr2710Asn <sup>(e)</sup>	Invariant	22	65	C15	PD	1	Tolerated	0.28	Disease causing	1	rs199700485	This study			
39	c.8914G>A	p.Asp2972Asn <sup>(b)</sup>	Invariant	24	23	C0	PD	1	Deleterious	0	Disease causing	1	rs150189496 (MAF 0.03%) Likely Neutral <sup>(d)</sup>		7		
38	c.9548G>A	p.Arg3183Gln <sup>(e)</sup>	Invariant	27	43	C0	PD	1	Deleterious	0.05	Disease causing	1	(MAF 0.001/3) rs79648977		8		
													Likely Neutral <sup>(d)</sup>				
1	c.9815G>A	p.Arg3272His <sup>(c)</sup>	Invariant	29	29	C0	PD	1	Deleterious	0	Disease causing	1				This study	
3	c.9829C>T	p.Arg3277Cys <sup>(e)</sup>	Invariant	29	180	C15	PD	1	Deleterious	0.04	Disease causing	1	Likely hypomorphic <sup>(d)</sup>		9		
42	c.9884A>G	p.Asn3295Ser	Invariant	29	46	C0	PD	0.999	Tolerated	0.43	Disease causing	0.999	Indeterminate <sup>(d)</sup>		8		
6	c.11834C>T	p.Thr3945Met	Highly conserved	43	81	C45	PD	1	Deleterious	0	Disease causing	0.959				This study	
29	c.12074A>G	p.Glu4025Gly	Invariant	44	98	C0	PD	1	Deleterious	0.05	Disease causing	1				This Study	
19	c.12161C>T	p.Ser4054Phe <sup>(c)</sup>	Moderately conserved	45	155	C15	PD	0.988	Deleterious	0.02	Polymorphism	0.777				This study	
8	c.12460C>T	p.Arg4154Cys	Invariant	46	180	C25	PD	1	Deleterious	0	Disease causing	1	Likely Pathogenic <sup>(d)</sup>		10		
39	c.12460C>T	p.Arg4154Cys <sup>(b)</sup>	Invariant	46	180	C25	PD	1	Deleterious	0	Disease causing	1	Likely Pathogenic <sup>(d)</sup>		10		
31	c.12460C>T	p.Arg4154Cys	Invariant	46	180	C25	PD	1	Deleterious	0	Disease causing	1	Likely Pathogenic <sup>(d)</sup>		10		

(a) PD : Probably damaging, PoD : Possibly damaging, B : Benign; (b) These three variations were identified in the unaffected father of case #40, but segregation could not be studied; (c) These two variations were identified in two probands, but we can not know whether they were transmitted or appeared *de novo*, as DNA from the unaffected parent was unavailable.  
(d) pkdb.mayo.edu/ ; (e) variants found in our in house database

**Supplementary Table 3 : Other *PKD1* missense variations identified in our cohort of adult ADPKD patients.**

Variation Number #	Nucleotide change	Effect on protein	Position on PC-1 orthologs	Exon	Grantham Distance	Align GVGD		Polyphen		SIFT		Mutation Taster		Reference
						Class	Prediction <sup>(a)</sup>	Score	Prediction	Score	Prediction	Probability		
1	c.6968T>G	p.Val2323Gly	Moderately conserved	16	109	C0	PD	0.997	Deleterious	0	Disease causing	1	This study	
2	c.7429C>T	p.Arg2477Cys	Moderately conserved	18	180	C0	PD	0.999	Deleterious	0.01	Disease causing	0.929	This study	
3	c.11014C>T	p.Arg3672Trp		37	101	C35	PD	0.999	Deleterious	0.02	Polymorphism	0.999	This study	
4	c.6850C>T	p.Pro2284Ser	Invariant	15	74	C0	PD	1	Deleterious	0	Disease causing	1	This study	
5	c.10043G>A	p.Arg3348Gln	Invariant	30	43	C35	PD	1	Deleterious	0.05	Disease causing	0.999	Bataille, 2011	
6	c.10351G>A	p.Asp3451Asn	Invariant	33	23	C15	PD	0.975	Deleterious	0	Disease causing	0.999	This study	
7	c.6173A>G	p.Gln2058Arg	Invariant	15	43	C0	PD	1	Deleterious	0	Disease causing	1	This study	
8	c.9898G>A	p.Gly3300Arg	Invariant	29	125	C65	PD	0.972	Tolerated	0.13	Disease causing	1	Cornec-Le Gall, 2013	
9	c.7693G>A	p.Ala2565Thr	Invariant	19	64	C0	PD	0.964	Deleterious	0.04	Disease causing	1	This study	
10	c.5038G>A	p.Gly1680Ser	Invariant	15	58	C55	PD	1	Tolerated	0.12	Disease causing	1	This study	
11	c.5111G>A	p.Gly1704Asp	Invariant	15	94	C65	PD	1	Tolerated	0.13	Disease causing	1	This study	
12	c.3277C>T	p.His1093Tyr	Invariant	15	83	C65	PD	0.998	Tolerated	0.05	Disease causing	0.973	Rossetti, 2007	
13	c.11675G>A	p.Arg3892His	Invariant	42	29	C25	PD	1	Tolerated	0.06	Disease causing	0.983	This study	
14	c.12424G>A	p.Gly4142Ser	Highly conserved	45	56	C55	PD	1	Deleterious	0	Disease causing	1	This study	
15	c.12413G>C	p.Arg4138Pro	Invariant	45	103	C35	PD	0.999	Deleterious	0.02	Polymorphism	0.558	This study	
16	c.10982C>T	p.Ala3661Val	Invariant	37	64	C65	PD	1	Deleterious	0	Disease causing	1	This study	
17	c.1823A>G	p.Gln608Arg	Invariant	9	43	C35	PD	0.998	Deleterious	0	Disease causing	0.999	This study	
18	c.7409C>T	p.Pro2470Leu	Invariant	18	98	C0	PD	1	Deleterious	0	Disease causing	0.999	This study	
19	c.8041C>T	p.Arg2681Cys	Moderately conserved	22	180	C25	PD	0.998	Deleterious	0.03	Disease causing	0.532	This study	
20	c.6439C>T	p.Arg2147Trp	Moderately conserved	15	101	C15	PD	0.997	Deleterious	0.03	Polymorphism	0.991	This study	

**Supplementary Table 4 : Non conservative variations identified in *PKHD1* in our cohort of early ADPKD**

Case #	Nucleotide change	Effect on protein	Exon	Grantham Distance	Align GVGD		PolyPhen		SIFT		Mutation taster		Remarks
					Class	Prediction <sup>(a)</sup>	Score	Prediction	Score	Prediction	Probability		
29 39 (mother) 4 20	c.1473C>A c.3259G>A c.9629C>G c.9689del	p.His491Gln p.Val1087Met p.Ser3210Cys p.Asp3230Valfs*34	16 29 58 58	24 21 112	C0 C0 C0 PD	PoD PD PD 1	0.506 0.988 0.988 0	Deleterious Deleterious Deleterious Deleterious	0.04 0.02 0.01	Polymorphism Polymorphism Disease causing	0.957 0.881 0.566	rs368613297 rs141081295	

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Homo sapiens	PSVGTFTNIIATAEVNEQSADQSIFTYVQLIEGLQVVG-----GGYFPTTMHTYQLQAVVR	1657
Macaca mulatta	PSVGTFTNIIATAEVNEQSADQSIFTYVQLIEGLQVAG-----CGSTYFTTMHTAQLQAVVR	1362
Canis familiaris	PSVGTFTNIIATAEVNEQSADQSIFTYVQLHIEGLQVAG-----GCCFFTTMHTYQLQAVVS	1654
Mus musculus	PSVGTFTNIIATAEVNEQSADQSIFTYVQLIEGLQVVG-----GCCFFTTMHTYQLQAVVR	1650
Rattus norvegicus	PSVGTFTNIIATAEVNEQSADQSIFTYVQLIEGLQVVG-----GCCFFTTMHTYQLQAVVR	1641
Monodelphis domestica	PSVGTFTNIIATAEVNESSQSADQSIFTYVQLIEGLQMLG-----GCCFFTTMHTYQLQAVVR	1647
Gallus gallus	PSVGTFTNIIATAEENLSEQSADQSIFTYVQLIEGLQVAS-----LLDYFFTTMHTLHLAVVR	1595
Xenopus	RSVGTFTNIVSTAEEVNQSACQQFSVVTYVLEATEGLHVTSLDVNCFTTMSLQLQADVY	1576

p.Asp1332Asn                    p.Thr1344Met

p.Val1611Ile

p.Gly1944Arg

p.Gln2058Arg

	N
<i>Home sapiens</i>	<i>ELVCPSCSLQFTLHKLEAMHNLILQIAETTAQPTVPTTAIGDCLSLINLTGDLIHLIASLDVRAPOP</i> 2736
<i>Macaca mulatta</i>	<i>ELVCPSCSLQFTLHKLEAMHNLILQIAETTAQPTVPTTAIGDCLSLINLTGDLIHLIASLDVRAPOP</i> 1638
<i>Cani familiaris</i>	<i>ELVCPSCSLQFTLHKLEAMHNLILQIAETTAQPTVPTTAIGDCLSLINLTGDLIHLIASLDVRAPOP</i>
<i>Mus musculus</i>	<i>ELMCSCSLQFTLHKLEAMHNLILQIAETTAQPTVPTTLDLISLNLTGDLIHLIASLDVRAPOP</i> 2719
<i>Rattus norvegicus</i>	<i>ELMCSCSLQFTLHKLEAMHNLILQIAETTAQPTVPTTLDLISLNLTGDLIHLIASLDVRAPOP</i> 2719
<i>Monodelphis domestica</i>	<i>EFYPCSCSLQFTLHKLEAMHNLILQIAETTAQPTVPTTLDLISLNLTGDLIHLIASLDVRAPOP</i> 2719
<i>Dallus galulus</i>	<i>ELVCPSCSLQFTLHKLEAMHNLILQIAETTAQPTVPTTLDLISLNLTGDLIHLIASLDVRAPOP</i> 2669
<i>Xenopus</i>	<i>KLECAACQWHTLSLULETHMSLILQNETTGGTGTNTPTTLADMLIMINGDGLIHLWNTNPPrYKMD</i> 2645

		N
Homo sapiens	AAAGHLQLQNYTLTDLGHYLSEEEPEPYLAVLYHLSEPPNMEHCNSASRP1PESLOGADHPY	2976
Macacus mulatta	AAAGHLQLQNYTLTDLGHYLSEEEPEPYLAVLYHLSEPPNMEHCNSASRP1PESLOGADHPY	1875
Canis familiaris	AAGHLQLQTYTTLTDLSEEPYLPPEPYLAVLYFDPSVGPMPMEHCNSASRP1SILELAGDHPY	2969
Mus musculus	QAGHLQLJPTTIVNLSEEPYLPPEPYLAVLYSQVSPMEYCNSASRP1SILEVLAGDHPY	2964
Rattus norvegicus	QAGHLQLJPTTIVNLSEEPYLPPEPYLAVLYSQVSPMEYCNSASRP1SILEVLAGDHPY	2956
Monodelphis domestica	EAGHLQLPTTIVNLSEEPYLPPEPYLAVLYSQVSPMEYCNSASRP1SILEVLAGDHPY	2959
Gallus gallus	EAGHLQLPTTIVNLSEEPYLPPEPYLAVLYSQVSPMEYCNSASRP1SILEVLAGDHPY	2900
Xenopus	NAPLH1QTYVVDQDEYVLSSEEEPEPYLAVLYHLSEPPHNPQYCTMD1QG1CMGD1LSQDHDHY	2876

p.Thr2710Asm

p.Asp2972Asn

	Q
<i> Homo sapiens</i>	DRAFHNSL1DIFIATPHSLGNSVVKWVHDNGLSPANFIQHVIVLDLTQARSAAFLVM 3216
<i> Macaca mulatta</i>	DRAFHNSL1DIFIATPHSLGNSVVKWVHDNGLSPANFIQHVIVLDLTQARSAAFLVM 2115
<i> Canis familiaris</i>	DRAFHNSL1DIFIATPHSLGNSVVKWVHDNGLSPANFIQHVIVLDLTQARSAAFLVM 3209
<i> Mus musculus</i>	DRAFHNSL1DIFIATPHSLGNSVVKWVHDNGLSPANFIQHVIVLDLTQARSAAFLVM 3204
<i> Rat norvegicus</i>	DRAFHNSL1DIFIATPHSLGNSVVKWVHDNGLSPANFIQHVIVLDLTQARSAAFLVM 3196
<i> Monodelphis domestica</i>	ESAFHNSL1DIFIATQCGSLGVVKWVHDNGLSPANFIQHVIVLDLTQGSCKEYFLVM 3199
<i> Gallus gallus</i>	ENAFHNSL1DIFIATQCGSLGVVKWVHDNGLSPANFIQHVIVLDLTQGSCKEYFLVM 3140
<i> Xenopus</i>	DNTFHNSL1DIFIATQCGSLGVVKWVHDNGLSPANFIQHVIVLDLTQGSCKEYFLVM 3116

	H
<i>Homo sapiens</i>	DULSVETEANGGLVEREVIAAASDAALLFPRFLLVAELQGKFHDHIVLMSUDRPPRSSFP 3276
<i>Macaca mulatta</i>	DULSVETEANGGLVEREVIAAASDAALLFPRFLLVAELQGKFHDHIVLMSUDRPPRSSFP 2175
<i>Canis familiaris</i>	DULSVETEANGGLVEREVIAAASDAALLFPRFLLVAELQGKFHDHIVLMSUDRPPRSSFP 3269
<i>Mus musculus</i>	DULSVETEANGGLVEREVIAAASDAALLFPRFLLVAELQGKFHDHIVLMSUDRPPRSSFP 3264
<i>Rattus norvegicus</i>	DULSVETEANGGLVEREVIAAASDAALLFPRFLLVAELQGKFHDHIVLMSUDRPPRSSFP 3256
<i>Monodelphis domestica</i>	DULSVETEANGGLVEREVIAAASDAALLFPRFLLVAELQGKFHDHIVLMSUDRPPRSSFP 3259
<i>Gallus gallus</i>	DULSVETEEDGGGLVEREVIAAASDAALLFPRFLLVAELQGKFHDHIVLMSUDRPPRSSFP 3209
<i>Xenopus</i>	DULSVGESEEGGRVEREVIAAASEMELKFRSIIPEVAEQGVSHVWLSMDRPPRSSFP 3176

p.Arg3183Gln

p.Arg3272His

	C	S
Homo sapiens	RIGQATCCVLLCIFLFLGAGANAVYVGVGDAYSAYSTGHVSRSLPLS3VTDVAVGLVS3SVVTPV	3336
Macaca mulatta	RIGQATCCVLLCIFLFGAGANAVYVGVGDAYSAYSTGHVSRSLPLS3VTDVAVGLVS3SVVTPV	2235
Canis familiaris	FVQVATCCVLLCIFLFGAGANAVYVGVGDAPSAGPVSTLPLS3VTDVAVGLVS3SVVTPV	3336
Mus musculus	FVQVATCCVLLCIFLFGAGANAVYVGVGDTPSYHSGPVFS1L3PVLGTDVAVGLVS3SVVTPV	3324
Rattus norvegicus	FVQVATCCVLLCIFLFGAGANAVYVGVGDTPSYHSGPVFS1L3PVLGTDVAVGLVS3SVVTPV	3324
Mondelphis domestica	FVQVATCCALLCIFLFGAGANAVYVGVGDPMVHNSHPS1L3PVLGTDVAVGLVS3SVVTPV	3319
Gallus gallus	FVQVATCCALLCIFLFGAGANAVYVGVGVHLS3GAVVPLFVNVDVAVGLVS3SVVTPV	3319
Xenopus	FVQVATCCALLCIFLFGAGANAVYVGVGDQSHVPLS3VSDVAVGHTVS3LVTPV	3236

	M	
Homo sapiens	AVAEATPHTTREGNVRVLRGAMARWHLVALTAVALVLAQGLADRRQTRPRFTGRPFPRF	3974
Macaca mulatta	AVAEATPHTTREGCNUFRPAAAMWHLVWLTAAATLVLAQGLADRRQTRPRFTGRPFPRF	2871
Canis familiaris	SVAEATPHTTREGCRAAQQGAMARWHLVALTAVALVLAQGLADRRQTRPRFTGRPFPRF	3966
Mus musculus	SVAEATPHTTREGCRAAQQGAMARWHLVALTAVALVLAQGLADRRQTRPRFTGRPFPRF	3959
Rattus norvegicus	SVAEATPHTTREGCRAAQQGAMARWHLVALTAVALVLAQGLADRRQTRPRFTGRPFPRF	3951
Macropodphilus domesticus	SVAEATPHTTREGCRAAQQGAMARWHLVALTAVALVLAQGLADRRQTRPRFTGRPFPRF	3956
Gallus gallus	VVAAELAQNGEQYQALYRAGAMQGQULLLILTTTVAATLVLHSLQSLADQGURGRYRFLRDFPRF	3896
Xenopus	VVSESLLLRQKQAYTFPRFQYQWQLLIVLAQTYVWVLSQASLADQGURGRYRFLRDFPRF	3889

p.Arg3277Cys p.Asn3295Ser

p.Thr3945Met

		G
<i>Homo sapiens</i>	TSFDQVAQLSSAAGLAASLLFLVKAQQQLRFLVRQNSVFGFTLICRALPELGVTLGLV	4034
<i>Macaca mulatta</i>	TSFDQVAQLSSAAGLAASLLFLVKAQQQLRFLVRQNSVFGFTLICRALPELGVTLGLV	2931
<i>Canis familiaris</i>	TSFEQVAQLSSAAGLAASLLFLVKAQQQLRFLVRQNSVFGFTLICRALPELGVGAALC	4026
<i>Mus musculus</i>	TSFDQVAQLGSVAGLAASLLFLVKAQQQLRFLVRQNSVFGFTLICRALPELGVTLGLV	4019
<i>Rattus norvegicus</i>	TSFDQVAQLGSVAGLAASLLFLVKAQQQLRFLVRQNSVFGFTLICRALPELGVTLGLV	4011
<i>Monodelphis domestica</i>	TSFYDQVAQLSSAFASLAASLLFLMIIATAQQLFIRQWNSVFGFTLICRALPELGVTLGLL	4011
<i>Gallus gallus</i>	TNFYDQVAFLNTTFLSIAASLLFLIVQAQQLFIRQWNSVFGFTLICRALPELGVTLGLV	3956
<i>Xenopus</i>	VSLYDQVFLGNTHTLSASLLFLVFTAQQLFIRQWNSVFGFTLICRALPELGVTLGLV	3949

	F	
Homo sapiens	VIGVATAQALIQLVSSCCSDLSW-----VAQALLVLCPGTGLSTLCPAESU--	4080
Macaca mulatta	VIGVATAQALVLVSSCCSDLSW-----VAQALLVLCSGFGSLTLCPAESU--	2977
Canis familiaris	ALAVAYAQLVSSCCSDVSFS-----AAAATGGAGGAACTTLYN-----	4072
Mus musculus	LLGVYAAMAILVAGGADLTLYN-----MARAFLVLPGAAVPTLCPSESW--	4065
Rattus norvegicus	LLGVYAAMAILVAGGADLTLYN-----MARAFLVLPGAAVPTLCPSESW--	4057
Monodelphis domestica	VILAVATTCFLMFLLSSCCSDLSW-----HGNDLFLLPAGGDHVCPSEWF-	4062
Gallus gallus	VILLAYAQLFLFLLSSSSESFBS-----VGSSLLILLIANWVSVLICPDSS--	4002
Xenopus	GLIVVYALQFLVFLACLCLVPEGUHSHLTLIMSDYIYHNPGLASVYNGPPGLCSELWQ	4009

p.Glu4025Gly

p.Ser4054Phe

	C
<i>Homo sapiens</i>	MGLS1VKEFHRVHFRVGEMLPLPSIIRRSGSRSKVSVDPPVPPGAGSDASHH--STTSSQLDGLS 4198
<i>Macaca mulatta</i>	MGLS1VKEFHRVHFRVGEMLPLPSIIRRSGSRSKVSVDPPVPPGAGSDASHH--STTSSQLDGLS 3095
<i>Canis familiaris</i>	MGSF1VKEFHRVHFRVGEMLPLPSIIRRSGSRSKSPDADPPGAGSDASHH--STTSSQLDGLS 4190
<i>Mus musculus</i>	MGSF1VKEFHRVHFRVGEMLPLPSIIRRSGSRSKSPFVPPVPGSSGAEASHH--STTSSQPDGGS 4183
<i>Rattus norvegicus</i>	MGTFTVKEFHRVHFRVGEMLPLPSIIRRSGSRSKSPFVPPVPGSSGAEASHH--STTSSQPDGGS 4183
<i>Monodelphis domestica</i>	MGSF1VKEFHRVHFRVGEMLPLPSIIRRSGSRSKSSQDPSVPPGAGSDASHH--STTSSQLDGMS 4119
<i>Gallus gallus</i>	MGSF1VKEFHRVHFRVGEMLPLPSIIRRSGSRSKSSQDPSVPPGAGSDASHH--STTSSQLDGMS 4119
<i>Xenopus</i>	HGVSEVKEFHRVHFRVGEMLPLPSIIRRSGSRSKSSQDPSVPPGAGSDASHH--STTSSQLDGSL 4129

Supplementary Figure : multiple sequence alignments at the positions of the identified additional variations