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	*PKD1*	1 to 5	c.1-?_1201+?del (*PKD1*)		large rearrangement	This study
13	*PKD1*	5	c.1010_1013dup		frameshift	This study
29	*PKD1*	11	c.2582G>A	p.Trp861*	nonsense	[1]
17	*PKD1*	11	c.2833_2834del		frameshift	[1]
20	*PKD1*	14	c.3202del		frameshift	This study
1	*PKD1*	15	c.4804del		frameshift	This study
22	*PKD1*	15	c.5764C>T	p.Gln1922*	nonsense	[2]
31	*PKD1*	15	c.5873G>A	p.Trp1958*	nonsense	This study
7	*PKD1*	15	c.6472C>T	p.Gln2158*	nonsense	[3]
35	*PKD1*	15	c.6472C>T	p.Gln2158*	nonsense	[3]
18	*PKD1*	15	c.6548_6551del	p.Thr2183Serfs*28	frameshift	This study
39	*PKD1*	15	c.6727_6730del	p.Gln2243Alafs*6	frameshift	[1]
34	*PKD1*	25	c.8998del	p.Arg3000Alafs*74	frameshift	This study
16	*PKD1*	25	c.9089_9096del	p.Leu3030Profs*36	frameshift	This study
42	*PKD1*	33	c.10232G>A	p.Trp3411*	nonsense	This study
40	*PKD1*	33	c.10343del	p.Pro3448Glnfs*25	frameshift	[1]
41	*PKD1*	33	c.10343del	p.Pro3448Glnfs*25	frameshift	[1]
28	*PKD1*	41	c.11538-2A>G		splicing	[1]
27	*PKD1*	42	c.11713-2A>G		splicing	This study
38	*PKD1*	42	c.11614G>T	p.Glu3872*	nonsense	[3]
32	*PKD1*	43	c.11884C>T	p.Gln3962*	nonsense	This study
26	*PKD1*	43	c.12003+1G>A		splicing	[1]
25	*PKD1*	45	c.12440dup	p.Glu4148Glyfs*9	frameshift	This study
14	*PKD1*	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[a]	Score	Prediction	Score	Prediction	Probability		
37	*PKD1*	c.689G>C	p.Cys230Ser	Invariant	5	112	C0	B	0.99	Deleterious	0	Disease causing	0.995	Highly Likely pathogenic[b]	[2]
6	*PKD1*	c.2180T>C	p.Leu727Pro	Invariant	11	98	C65	PD	1	Deleterious	0.01	Disease causing	1	Highly Likely pathogenic[b]	[2]
8	*PKD1*	c.7108T>A	p.Cys2370Ser	Invariant	17	112	C0	PD	1	Deleterious	0	Disease causing	1	Highly Likely pathogenic[b]	[2]
36	*PKD1*	c.7115C>G	p.Ser2372Cys	Invariant	17	112	C65	PD	1	Deleterious	0	Disease causing	1	Likely pathogenic[b]	[1]

(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[a]	Score	Prediction	Score	Prediction	Probability		
21	*PKD1*	c.5517G>T	p.Trp1839Cys	Invariant	15	215	C0	PD	1	Deleterious	0	Disease causing	1		This study
19	*PKD1*	c.7978G>T	p.Asp2660Tyr	Invariant	21	160	C15	PD	1	Deleterious	0.01	Disease causing	1		This study
24	*PKD1*	c.8497C>T	p.Pro2833Ser	Invariant	23	74	C65	PD	1	Deleterious	0	Disease causing	1		This study
23	*PKD1*	c.9562A>G	p.Asn3188Asp	Invariant	27	23	C15	PD	1	Deleterious	0	Disease causing	1		This study
12	*PKD1*	c.9563A>T	p.Asn3188Ile	Invariant	27	149	C65	PD	1	Deleterious	0	Disease causing	1		This study
11	*PKD1*	c.11969T>G	p.Leu3990Arg	Invariant	43	102	C65	PD	1	Deleterious	0.01	Disease causing	0.966		This study
2	*PKD2*	c.964C>G	p.Arg322Gly		4	125	C65	PD	0.999	Deleterious	0	Disease causing	1	Highly Likely pathogenic[b]	[4]
15	*PKD2*	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	*PKD1*	21	c.8017-3C>G		Splicing[c]		This study
10	*PKD1*	27	c.9568G>A		Splicing[d]		This study
30	*PKD1*	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[a]	Score	Prediction	Score	Prediction	Probability		
4	*PKD1*	c.2534T>C	p.Leu845Ser	Invariant	11	145	C65	PD	1	Deleterious	0.01	Disease causing	0.997	Highly Likely pathogenic[b]	[5]
9	*PKD1*	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

						Align GVGD	Polyphen		SIFT		Mutation Taster			
Case #	Nucleotide change	Effect on protein	Position on PC-1 orthologs	Exon	Grantham Distance	Class	Prediction[a]	Score	Prediction	Score	Prediction	Probability	Remarks	Reference
18	c.3994G>A	p.Asp1332Asn	Highly conserved	15	23	C15	PD	0.985	Deleterious	0	Disease causing	1	LikelyNeutral[d]	6
39	c.4031C>T	p.Thr1344Met[b]	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[e]	Invariant	22	65	C15	PD	1	Tolerated	0.28	Disease causing	1	rs199700485	This study
39	c.8914G>A	p.Asp2972Asn[b]	Invariant	24	23	C0	PD	1	Deleterious	0	Disease causing	1	rs150189496 (MAF 0.03%) Likely Neutral[d]	7
38	c.9548G>A	p.Arg3183Gln[e]	Invariant	27	43	C0	PD	1	Deleterious	0.05	Disease causing	1	rs79648977 (MAF 0.001/3) Likely Neutral[d]	8
1	c.9815G>A	p.Arg3272His[c]	Invariant	29	29	C0	PD	1	Deleterious	0	Disease causing	1		This study
3	c.9829C>T	p.Arg3277Cys[e]	Invariant	29	180	C15	PD	1	Deleterious	0.04	Disease causing	1	Likely hypomorphic[d]	9
42	c.9884A>G	p.Asn3295Ser	Invariant	29	46	C0	PD	0.999	Tolerated	0.43	Disease causing	0.999	Indeterminate[d]	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[c]	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[d]	10
39	c.12460C>T	p.Arg4154Cys[b]	Invariant	46	180	C25	PD	1	Deleterious	0	Disease causing	1	Likely Pathogenic[d]	10
31	c.12460C>T	p.Arg4154Cys	Invariant	46	180	C25	PD	1	Deleterious	0	Disease causing	1	Likely Pathogenic[d]	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.

						Align GVGD	Polyphen		SIFT		Mutation Taster		
Variation Number #	Nucleotide change	Effect on protein	Position on PC-1 orthologs	Exon	Grantham Distance	Class	Prediction[(a)]	Score	Prediction	Score	Prediction	Probability	Reference
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

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

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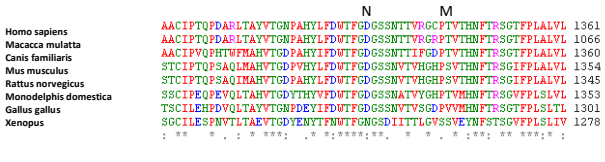

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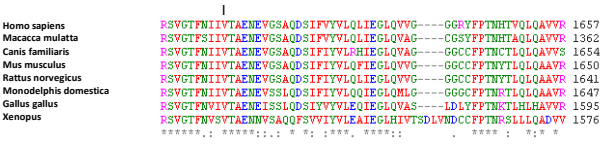

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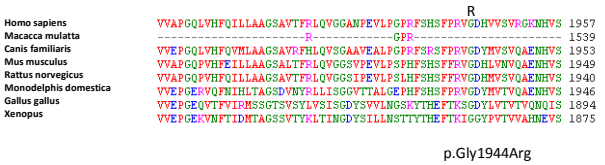

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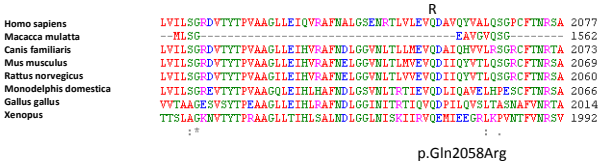

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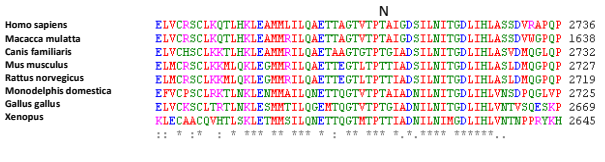

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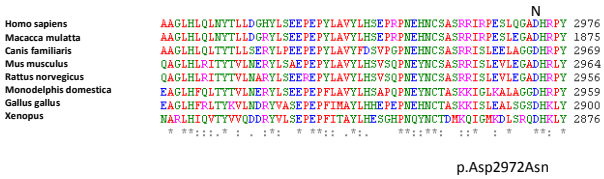

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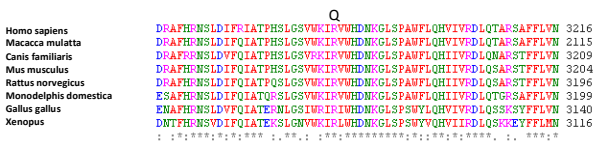

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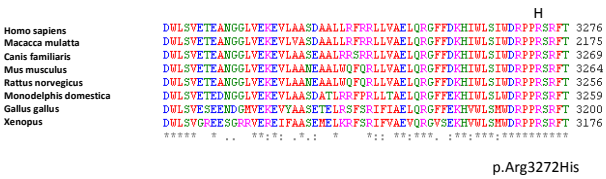

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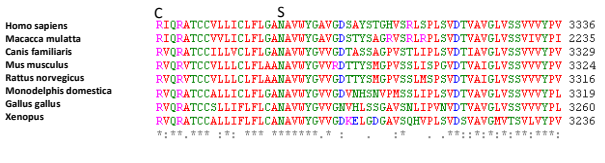

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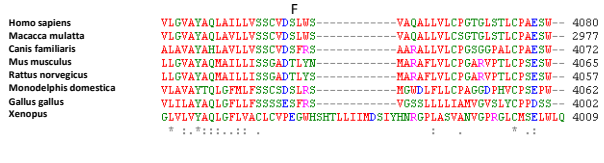

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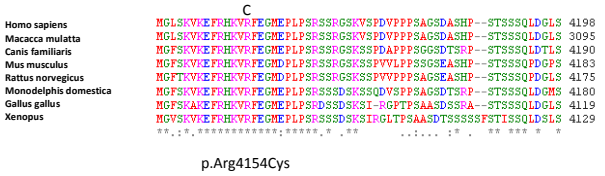

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Supplementary Figure : multiple sequence alignments at the positions of the identified additional variations