

**Research Paper** 



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# Spectrum and Classification of ATP7B Variants in a Large Cohort of Chinese Patients with Wilson's Disease Guides Genetic Diagnosis

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#### Abstract

**Background:** Wilson's disease (WD) is an autosomal recessive disorder of copper metabolism caused by *ATP7B* pathogenic mutations. The symptoms of WD can be effectively prevented if the affected individuals are identified and intervened early. However, clinical utility of this molecular analysis is challenging due to hundreds of variants with various clinical effects in the gene. Here, we aim to describe the spectrum of *ATP7B* variants and assess their clinical effects in the Han Chinese population.

**Methods:** The *ATP7B* gene was directly sequenced in 632 unrelated WD patients and 503 unrelated healthy individuals. The effects of identified variants were classified according to the American College of Medical Genetics and Genomics (ACMG) standards and guidelines. Different frequency of variants observed in both cases and controls were tested using Chi-square or Fisher's exact tests.

**Results:** We detected 161 non-synonymous variants in these 632 WD patients, 58 of which were novel. Among these variants, 78, 64, 8, 4, and 7 were classified as 'pathogenic variants', 'likely pathogenic variants', 'variants with uncertain significance', 'likely benign variants', and 'benign variants', respectively. Ninety percent (569/632) of these WD patients can be genetically diagnosed with two or more 'pathogenic' or 'likely pathogenic' variants. The 14 most common disease-causing variants were found at least once in 94% (537/569) of genetically diagnosed patients.

**Conclusions:** These data expand the spectrum of *ATP7B* variants and facilitate effective screening for *ATP7B* variants for early diagnosis of WD and development of individualized treatment regimens.

Key words: Wilson's disease; ATP7B; variants classification.

# Introduction

Wilson's disease (WD, OMIM #277900), or progressive hepatolenticular degeneration, is an autosomal recessive disease caused by pathogenic mutations within the *ATP7B* gene. <sup>1-3</sup>*ATP7B* encodes a P-type ATPase that is involved in the transport of copper into the plasma protein ceruloplasmin (Cp) and in the ex-

cretion of copper from the liver. ATP7B protein malfunction leads to massive accumulation of copper in the liver, brain, and other tissues. The accumulation of copper in these areas can present a wide spectrum of symptoms, including liver cirrhosis; neuronal degeneration of the brain, particularly in the basal ganglia; Kayser-Fleischer (K-F) rings at the corneal limbus; and kidney damage.<sup>4</sup> The incidence of WD is estimated to be 1 in 30,000 individuals, and the heterozygous carrier rate is about 1 in 90 among many ethnic groups.<sup>5</sup> However, a recent study identified the genetic prevalence of WD as 1:7,026 in the United Kingdom by sequencing ATP7B in 1000 control subjects,6 much higher than the typically reported prevalence of WD of 1:30,000. In addition, WD is thought to be more frequent in Asian populations. The presumed prevalence of WD is approximately 1 in 3,000 in the Korean population<sup>7</sup> and the expected frequency of WD is 1 in 5,400 in the Hong Kong Han Chinese population.8

WD is among a limited number of inherited diseases for which symptoms can be prevented if the affected individuals can be identified and intervened early. However, accurate and early clinical diagnoses are often difficult to make due to the wide array of phenotypic variations.<sup>9</sup> While genetic analysis is feasible, its clinical utility has been limited due to more than 700 *ATP7B* reported variants with various clinical effects (https://portal.biobase-international.com/hgmd/pro/gene.php?gene=ATP7B, Human Gene Mutation Database Professional, access date: 20 October, 2015). Therefore, better understanding of the spectrum of *ATP7B* variants and the clinical effects of these variants are necessary for clinical application.

Here, we reported variants identified from a study that directly sequenced the *ATP7B* gene in 632 consecutively treated WD patients at three Chinese academic medical centers between 2004 and 2015, and 503 unrelated phenotypically normal individuals. The clinical effects of identified variants were classified according to the American College of Medical Genetics and Genomics (ACMG) standards and guidelines.

## **Subjects and Methods**

#### **Participants**

Consecutive patients who sought for diagnosis and treatment of WD between January 15, 2004 and April 30, 2015 at the Departments of Neurology at three leading Chinese academic medical centers were recruited, including Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou; First Affiliated Hospital, Fujian Medical University, Fuzhou; Huashan Hospital, Fudan University, Shanghai. Each patient was examined by at least two senior neurologists, including medical history review and physical exams. The patients were clinically diagnosed with WD according to the diagnostic criteria described previously.<sup>4</sup> Blood samples of 632 unrelated patients (346 males and 286 females, aged 9 to 56) who have average onset age of  $18.5 \pm 0.6$  ranging from 3 to 48 years and 503 unrelated phenotypically normal controls with no known family history of WD were included in the study. Family history were detected in 16 out of 632 WD patients. All participants are of Han Chinese descent. The probands, or their legal guardians, provided informed consents. This study was approved by three institutional review boards.

# Direct DNA Sequencing for Mutation Analysis of ATP7B

Genomic DNA was isolated from peripheral blood lymphocytes using a DNA isolation kit (Qiagen Inc, Valencia, CA). All 21 exons and their flanking regions as well as the 5'-untranslated region (UTR) and promoter regions of the ATP7B gene were sequenced. Exon 2, which is 1,234 base pair (bp) in length, was covered by three overlapping PCR fragments. The primer sequences, annealing temperatures, and sizes of the PCR products of exons 1, 2, 4, 16, and 18 were listed in Table S1. Information related to the remaining primers has been described previously.<sup>10</sup> PCR amplification and direct sequencing were performed as previously reported.<sup>11</sup> Obtained sequences were compared, and nucleotide changes were numbered according to their position in ATP7B mRNA (NM\_000053). Novel variants were further confirmed by sequencing both the forward and reverse strands. The sequence variants were interpreted and classified according to ACMG Standards and Guidelines.12

#### **Statistical Analysis**

Different frequency of variants observed in both WD patients and controls was tested using Chi-square test or the Fisher's exact test (for variants with the expected number of subjects below 5). The Bonferroni correction was used to declare statistical significance.

#### Results

#### Variants identified in the ATP7B Gene

A total of 173 variants in the coding region and the adjacent splice sites of the *ATP7B* gene were identified among 632 unrelated WD patients and 503 controls, including 161 non-synonymous and 12 synonymous variants. Among the 161 non-synonymous variants, 150 were detected only in WD patients and 11 were detected in both WD patients and normal controls. To assess link of the latter group of variants with WD, we compared allele frequency for 10 of these 11 variants between WD patients and controls (one of the 11 variants, p.R778L, was excluded because it is a well-established pathogenic variant<sup>13</sup>). Three variants (p.I390V, p.T935M, and p.V1106I) were considerably more common in WD patients than controls and the differences reached a statistical significance level (p<0.005) after adjusting for 10 multiple tests (0.05/10) (**Table 1**). The estimated odds ratios (ORs) of these three variants greater than 10 (p.I390V, OR=11.26; p.T935M, OR=77.04; p.V1106I, OR=10.44). For the remaining 7 variants, the allele frequency was similar between cases and controls (p>0.005), with ORs close to 1.00. Homozygotes in controls were found for 5 of these 7 variants (**Table 1**).

Among 12 synonymous variants, 5 were novel, including c.2145c>T (p.Y715Y), c.3243G>A (p.G1287G), (p.E1081E), c.3861C>G c.4014T>A (p.I1338I), c.4194c>T (p.S1398S). The remaining varibeen previously ants have identified (http://asia.ensembl.org/Homo\_sapiens/Transcript /Sequence\_cDNA?db=core;g=ENSG00000123191;r=1 3:51932673-52011494;t=ENST00000242839, access date: 20, October, 2015), including c.747G>A (p.L249L, rs554554415), c.1620c>T (p.L540L,rs145798966), (p.F764F, c.2292c>T rs372979339), c.2310C>G (p.L770L, rs398123136), c.2973G>A (p.T991T, rs1801246), c.3009G>A (p.A1003A, rs1801247) and c.4251A>G (p.T1417T, rs546721020).

## **Classification of Variants**

Among 161 non-synonymous variants, 7 were similar between cases and controls (**Table 1**), thus classified as benign variants according to the ACMG Standards and Guidelines.<sup>12</sup> The remaining 154 non-synonymous variants were only observed in WD patients or significantly more frequent in WD patients (**Table 2**). They are distributed throughout the *ATP7B* gene exons 1 to 21 (**Figure 1**). Among these 154 non-synonymous variants, 18 (11.7%) are nonsense variants, 25 (16.2%) are small deletions or insertions, 11 (7.1%) are splice site variants, and 100 (64.9%) are missense variants. According to the ACMG Standards and Guidelines,12 18 nonsense variants can be classified as 'pathogenic variants'. Among 25 small deletions/insertions, three shift variants including c.2316\_2317insCTCTTTGTG (p.V772insLFV), c.2790\_2 792del(p.I930del) and c.4005 4006insTTATAATGGG TTGCG (p.G1335insLXWVA) can only be classified as 'likely pathogenic variants' due to its in-frame characteristics, other 22 ones can be classified as 'pathogenic variants' as well. For the 11 splice site mutations, six (c.51+1g>a, c.1543+1g>t, c.1708-1g>c, c.1870-2a>g, c.2356-1g>c, and c.3557-2a>g) are predicted to result in exon skipping and lead to the production of a defective protein, therefore can also be classified as 'pathogenic variants'. For the other five site variants (c.1543+4a>g, splice c.1708-5t>g, c.1946+5g>a, c.2447+5g>t, and c.3903+5g>a), because additional functional analysis is required to assess their impact on RNA and protein, they can be classified as 'variants with uncertain significance' at this stage. For the 100 missense variants (Table 3), 32, 61, 4, and 3 can be classified as 'pathogenic variants', 'likely pathogenic variants", 'likely benign variants", and 'variants with uncertain significance', respectively, based on results of SIFT, PolyPhen-2, 1000 Genomes Project, Exome Aggregation Consortium and the ACMG Standards and Guidelines. In total, among 161 non-synonymous variants, 78 are classified as 'pathogenic variants', 64 as 'likely pathogenic variants', 8 as 'variants with uncertain significance', 4 as 'likely benign variants' and 7 as 'benign variants'. Therefore, 142 variants could be considered as potential disease-causing variants ('pathogenic variants' and 'likely pathogenic variants') at this stage.

Table 1. The Allele Frequency of 10 Non-Synonymous Variants in 632 WD Patients and 503 Controls.

Variants		Со	ntrols			WD	Patients		Probabilities	
	Wildtype	Heterozygote	Homozygote	Allele	Wildtype	Heterozygote	Homozygote	Allele	-	OR(95%CI)
				Frequency				Frequency		
p.I390V	502	1	0	0.001	619	12	1	0.011	0.003*	11.256(1.478-85.743)
p.S406A	146	223	134	0.488	153	271	208	0.544	0.044	1.249(1.058-1.474)
p.L456V	150	240	113	0.463	157	304	171	0.511	0.085	1.211(1.026-1.430)
p.R832K	339	59	105	0.267	441	47	144	0.265	0.045	0.988(0.819-1.192)
p.I929V	488	15	0	0.015	624	8	0	0.006	0.042	0.421(0.178-0.997)
p.T935M	502	1	0	0.001	543	88	1	0.071	1.40E-22*	77.044(10.716-553.910)
p.R952K	164	261	78	0.415	206	335	91	0.409	0.862	0.978(0.826-1.157)
p.V1106I	502	1	0	0.001	619	13	0	0.010	0.0049*	10.444(1.364-79.969)
p.V1140A	195	240	68	0.374	258	286	88	0.366	0.706	0.965(0.813-1.146)
p.V1297I	498	5	0	0.005	628	4	0	0.003	0.520	0.636(0.17-2.373)

\*Based on Fisher's Exact test due to small observed number of variants.



Figure 1: (A) Schematic representation of the ATP7B gene with 21 exons. All here identified variants in WD patients with Chinese Han descent are visualized in the corresponding ATP7B protein regions. Fifty-eight novel variants are indicated in red characters. Cu 1~6, six copper binding domains; Tm 1~8, eight transmembrane domains; Td, a transduction domain converting the ATP hydrolysis energy to the impetus of transporting copper cation; Ch, the transmembrane cation channel; Ph, the phosphorylation domain; ATP loop/binding/hinge, the ATP binding domain. (B) Distribution of ATP7B variants is shown within 21 exons of ATP7B gene.

**Table 2.** One Hundred and Fifty-Four Non-Synonymous Variants were Only Observed in WD Patients or Significantly More Frequent inWD Patients.

Mutation analysis		Domain	Frequency of MU (%)	No. of patients		
Nucleotide mutation	Protein alteration	Exon	-		MU/MU	WT/MU
c.51+1g>a	Na	1	before Cu1	0.08	0	1
c.268_271del	p.K90FfsX10	2	Cu2	0.08	0	1
c.314C>A	p.S105X	2	Cu2	0.08	0	1
c.367delG	p. A123PfsX30	2	Cu2	0.08	0	1
c.525dupA	p.V176SfsX28	2	Cu2	1.50	1	17
c.588C>A	p.D196E	2	Cu2	0.40	0	5
c.592A>G	p.R198G	2	Cu2	0.08	0	1
c.695delC	p.P232QfsX30	2	Cu3	0.08	0	1
c.994G>T	p.E332X	2	Cu3/Cu4	0.55	0	7
c.1168A>G	p.I390V	2	Cu3/Cu4	1.11	1	12

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Mutation analysis			Domain	Frequency of MU (%)	No. of patients	
Nucleotide mutation	Protein alteration	Exon	-		MU/MU	WT/MU
c.1403_1416del	p.A468GfsX33	3	Cu4/Cu5	0.08	0	, 1
c 1426G>A	p A476T	3	$C_{114}/C_{115}$	0.08	0	1
c 1449 1456del	p.R483SfeX20	3	Cu5	0.16	0	2
c.1470C>A	p.C490X	3	Cu5	0.24	0	2
- 1521C>T	- OF11X	2	Cu5	0.24	0	3
c.1531C>1	p.Q511X	3	Cus	2.37	2	26
c.1543+1g>t	Na	3	Cu5	0.47	0	6
c.1543+4a>g	Na	3	Cu5	0.08	0	1
c.1544G>T	p.G515V	4	Cu5	0.08	0	1
c.1545delT	p.G515GfsX9	4	Cu5	0.08	0	1
c.1552_1553delTC	p.S518RfsX15	4	Cu5	0.08	0	1
c.1639C>T	p.Q547X	4	Cu5	0.08	0	1
c.1708-5t>g	Na	5	Cu6	1.03	1	11
c.1708-1g>c	Na	5	Cu6	1.50	2	15
c.1760C>T	p.T587M	5	Cu6	0.08	0	1
c.1782T>A	p.Y594X	5	Cu6	0.08	0	1
c 1803delC	n S602 AfsX46	5	Cu6	0.08	0	1
c 1817T>G	p.V606G	5	Cu6	0.16	0	2
c.1820.dup.A	p. F608VfcY2	5	Cub	0.16	0	2
19460 T	P.1008VISA2	5	Cuo	0.10	0	2
0.18460-1	p.K6161	5	Cub	0.08	0	1
c.18/0-2a>g	na	6	Cub	0.08	0	1
c.1925A>G	p.D642G	6	Cu6	0.08	0	1
c.1946+5g>a	na	6	Cu6/TM1	0.08	0	1
c.1950G>A	p.W650Term	7	Cu6/TM1	0.08	0	1
c.2038C>T	p.Q680X	7	Cu6/TM1	0.08	0	1
c.2043delC	p.S681SfsX15	7	TM2	0.08	0	1
c.2078C>G	p.S693C	7	TM2	0.16	0	2
c.2128G>A	p.G710S	8	TM2/TM3	0.08	0	1
c.2156A>G	p.Y719C	8	TM2/TM3	0.08	0	1
c.2157C>A	p.Y719X	8	TM2/TM3	0.24	0	3
c.2192T>A	p.V731E	8	TM3	0.08	1	0
c 2195T>C	p I 732P	8	TM3	0.08	0	1
c 2223T>A	p.V741X	8	TM3	0.08	0	1
c.22231277	p.1741A	0	TM2	0.00	0	1
222513-1	p.A7515	0		0.08	0	1
c.2261A>G	p.E754G	8	1M3/1M4	0.08	0	1
c.226/C>G	p.A/56G	8	TM3/1M4	0.08	0	1
c.2294A>G	p.D765G	8	TM4	0.24	0	3
c.2297C>T	p.T766M	8	TM4	0.16	0	2
c.2304dupC	p.M769HfsX26	8	TM4	0.87	0	11
c.2305A>G	p.M769V	8	TM4	0.08	0	1
c.2308C>T	p.L770F	8	TM4	0.08	0	1
c.2316_2317ins	p.V772insLFV	8	TM4	0.08	0	1
CTCTTTGTG						
c.2332C>T	p.R778W	8	TM4	0.16	0	2
c.2333G>T	p.R778L	8	TM4	29.67	64	247
c.2333G>A	p.R778Q	8	TM4	1.98	3	19
c.2336G>A	p.W779X	8	TM4	0.08	0	1
c.2341G>A	p.E781K	8	TM4	0.08	0	1
c.2356-1g>c	na	9	TM4/Td	0.08	0	1
c.2383C>T	p.L.795F	9	TM4/Td	0.08	0	1
c 2390C>T	n S797F	9	TM4/Td	0.08	0	1
c 2447+5g>t	Na	9	TM4/Td	0.08	0	1
c.2455C>T	n O819Y	10	TM4/Td	0.08	0	1
- 2525 4 > C	- D842C	10	TM4/10	0.08	0	1
C.2525A>G	p.D842G	10		0.08	0	1
c.2587C>1	p.18635	11	la	0.08	0	1
c.2605G>A	p.G869R	11	Id	0.16	0	2
c.2620G>C	p.A874P	11	Td/TM5	0.08	0	1
c.2621C>T	p.A874V	11	Td/TM5	3.56	3	39
c.2648_2649del	p.V883AfsX3	11	Td/TM5	0.08	0	1
c.2662A>C	p.T888P	11	Td/TM5	0.32	0	4
c.2668G>A	p.V890M	11	Td/TM5	0.16	0	2
c.2740C>T	p.Q914X	12	Td/TM5	0.08	0	1
c.2755C>G	p.R919G	12	Td/TM5	1.98	0	25
c.2790_2792del	p.I930del	12	TM5	0.47	0	6
c.2794 2795insGT	p.S932CfsX4	12	TM5	0.08	0	1
c.2804C>T	p.T935M	12	TM5	7.12	1	88
c 2810delT	n V937GfsX5	12	TM5	0.63	0	8
c 2827C>A	p. 69435	12	TM5	0.55	1	5
c 2828C > A	p.0730	12	TM5	2.00	- 1	26
- 2949CNT	P.3750	12	TME/TMA	<u></u>	-	1
0.20400/1	P. V 200F	14	11410/11410	0.00	U	1

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NeckendencingPolentic point of the sector of t	Mutation analysis		Domain	Frequency of MU (%)	) No. of patients		
235.1356.adpOSHIBA/S12TAG/TAG0.080123425.71p370710TAG0.080123425.4Ap370710TAG0.0701023425.4Ap370710TAG0.080123425.71p370710TAG0.080123507.71p370710TAG/FA0.060123507.71p3408710TAG/FA0.080123507.71p3408713TAG/FA0.080123507.71p3408713TAG/FA0.080123507.71p3408713TAG/FA0.080123507.71p3408714Ph0.080123507.71p3408714Ph0.080123507.71p3408714Ph0.080123507.71p3408714Ph0.080123507.71p3408714ATP sop0.80123507.71p3408714ATP sop0.80123507.71p3408714ATP sop0.80123507.71p3408714ATP sop0.80123507.71p3408715ATP sop0.80123507.71p3408715ATP sop0.80123507.71p3408715ATP sop	Nucleotide mutation	Protein alteration	Exon	-		MU/MU	WT/MU
238571501660.5701238571371660.7001238571381660.7001238571391660.8001238571391660.8001238571301660.8001238571301501660.800123857130150166/760.80012385713019713166/760.84012385713019713166/760.84012385713019713166/760.8401238571301971416601123857130197141719970.860123857130197141719970.860123857130197141719970.8601238571302971301141719970.860123857130297130197141719970.860123857130297130297130213011123857130297130297130213011123857130297130297130213011123857130297130297130213011123857130297130297130213011<	c.2853_2856del	p.Q951HfsX15	12	TM5/TM6	0.08	0	1
c2326ApSTPXDThéD.7D.6D.9D.0C3NOCTPSTPADD.66D.80DDC3NOCTPSTPADD.66/PhD.80DDC3NOCTPALOUTDD.66/PhD.80DDCANNOCAPALOUTDD.66/PhD.80DDCANNOCAPALOUTDD.66/PhD.80DDCANNOCAPALOUTDD.66/PhD.80DDCANNOCAPALOUTDD.66/PhD.80DDCANNOCAPALOUTDD.66/PhD.80DDCANNOCAPALOUTDDDDDDCANNOCAPALOUTDDDDDDCANNOCAPALOUTDDDDDDDCANNOCAPALOUTDDDDDDDCANNOCAPALOUTDDDDDDDDCANNOCAPALOUTDDDDDDDDDDDCANNOCAPALOUTDD<	c.2905C>T	p.R969W	13	TM6	0.08	0	1
constraintpip2/mitpip2/	c 2924C > A	n \$975Y	13	TM6	0.79	0	10
Segmentp388p388p488p1CMUCPAp4000T13TM6/Ph16.55656CMUCPApA000T13TM6/Ph0.6601CMUCPApA000T13TM6/Ph0.8801CMUCPApA000T13TM6/Ph0.8801CMUCPApA000T13TM6/Ph0.8801CMUCPApA000T14PA0.8801CMUCPApA000T14PA0.8801CMUCPApA000T14PA0.8801CMUCPApA000T14PA0.8801CMUCPApA000T14PA0.8801CMUCPApA000T14ATPsop0.8801CMUCPApA000T14ATPsop0.8801CMUCPApA000T14ATPsop0.8801CMUCPApA000T14ATPsop0.8801CMUCPApA000T14ATPsop0.8801CMUCPApA000T14ATPsop0.8801CMUCPApA000T14ATPsop0.8801CMUCPApA000T14ATPsop0.8801CMUCPApA000T15ATPsop0.8801CMUCPApA000T15ATPsop0.8801CMUCPA <t< td=""><td>c 2930C&gt;T</td><td>p.59701</td><td>13</td><td>TM6</td><td>0.08</td><td>0</td><td>10</td></t<>	c 2930C>T	p.59701	13	TM6	0.08	0	10
AMEPAODPAO	c 2957C>T	p.197741	13	TM6	0.08	0	1
LONG-5.JPLAUTJPLA	0075C>T	p.3900F	13		14 50	0	1
LAUDAAPAUDB	c.2975C>1	p.19992L	13	TM6/Ph	14.56	26	132
C3005C7pA1087jA1087jA1087jA1087jAc3005C7pA10817jATAM/PA0.8801c3024CpA10817jATAM/PA0.8403c3035C7pA10817jATAM/PA0.8403c3035C7pA10817jAPA0.8401c3035C7pA10817iAPa0.8401c3035C7pD1000AiAPa0.8401c3035C7pD1000AiAPa0.8601c3035C7pD1000AiAPa0.8601c3035C7pD1000AiAATPhorp0.8601c3035C7pD1007AiAATPhorp0.8601c3055C7pD1007AiAATPhorp0.8801c3055C7pD1007AiAATPhorp0.8801c3055C7pD1007AiSATPhorp0.8801c3055C7pD1007AiSATPhorp0.8801c3055C7pD1007AiSATPhorp0.8801c3055C7pD1087AiSATPhorp0.8801c3055C7pD11867AiSATPhorp0.8801c3055C7pD1187AiSATPhorp0.8801c3055C7pD1187AiSATPhorp0.8801c3055C6pD1187AiS	c.3007G>A	p.A10031	13	TM6/Ph	0.16	0	2
c300C>FIp<0008X13TMs/Ph0.0801C302A>Cp <l1018p< td="">13TMs/Ph0.0801C305C&gt;Tp<a1008v< td="">13TMs/Ph0.0801C305CAp<k1008< td="">14Ph0.0801C305CAp<h002t< td="">14Ph0.0801C305CAp&lt;1002T</h002t<></k1008<></a1008v<></l1018p<>	c.3008C>T	p.A1003V	13	TM6/Ph	0.08	0	1
cdS3ACpKI01713TM0/Ph0.1602CMMCCpAL018713TM0/Ph0.2403CMMCCpAL018N13TM0/Ph0.2403CMMCCpAL018N13Ph0.8801CMMCCpCG030014Ph0.8801CMMCCpUG37014Ph0.8801CMMCCpUG37014Ph0.8801CMMCCpUG37014Ph0.8601CMMCCpUG37014APP loop0.6611CMMCCpUG37014APP loop0.6611CMMCCpUG37014APP loop0.6611CMMCCpUG37014APP loop0.86011CMMCCpUG37015APP loop0.86101CMMCCpUG37015APP loop0.86101CMMCCpUG37015APP loop0.86101CMMCCpUG37015APP loop0.86101CMMCCpUG37016APP loop0.86101CMMCCpUG37016APP loop0.86111CMMCCpUG37016APP loop0.86111CMMCCpUG37016APP loop0.86111 <td>c.3010C&gt;T</td> <td>p.Q1004X</td> <td>13</td> <td>TM6/Ph</td> <td>0.08</td> <td>0</td> <td>1</td>	c.3010C>T	p.Q1004X	13	TM6/Ph	0.08	0	1
cbmlPCpl.nipP13Mb//h0.0801CSSC-Tp.K102814Mr.0.8501CSSMAGp.K102814P.0.4001CSSMAGp.G1030.145.1114P.0.4001CSSMACp.G1030.145.1114N0.8001CSSMACp.G1037.1114N0.8101CSSMACp.G1037.1114NThoop0.1610CJUEC-Tp.R1041.1114ATP loop0.1611CJUEC-Tp.R1041.1114ATP loop0.2411CJUEC-Tp.R1041.1114ATP loop0.2411CJUEC-Tp.R1041.1114ATP loop0.2411CJUEC-Tp.R1041.1114ATP loop0.2411CJUEC-Tp.R1041.1115ATP loop0.8601CJUEC-Tp.R1047.1115ATP loop0.8601CJUEC-Tp.R11261.1115ATP loop0.8601CJUEC-Tp.R11261.1116ATP loop0.8601CJUEC-Tp.R11261.1116ATP loop0.8601CJUEC-Tp.R11261.1116ATP loop0.8601CJUEC-Tp.R11261.1116ATP loop0.8601CJUEC-Tp.R11261.1116ATP loop0.86t	c.3029A>C	p.K1010T	13	TM6/Ph	0.16	0	2
cb885-71p.Al028p.Al028p.Alp.Al028p.Alp.	c.3044T>C	p.L1015P	13	TM6/Ph	0.08	0	1
c)NNACCPK1000PK10.0801CAMSATPG1000A'SM14Ph0.4001CAMSATPG1000A'SM14Ph0.8001CAMSATPG1003A'SM14Ph0.8001CAMSATPG1033A'14Ph0.8601CAMSATPG1033A'14Ph0.8610CAUGATPG103A'14ATPloop0.8610CAUGATPLINUT14ATPloop0.8601CAUGATPLINUT14ATPloop0.8601CAUGATPLINUT14ATPloop0.8601CAUGATPLINUT15ATPloop0.8610CAUGATPLINUT15ATPloop0.8610CAUGATPLINUT15ATPloop0.8611CAUGATPLINUT15ATPloop0.8611CAUGATPLINUT15ATPloop0.8611CAUGATPLINUT16ATPloop0.8611CAUGATPLINUT16ATPloop0.8611CAUGATPLINUT16ATPloop0.8611CAUGATPLINUT16ATPloop0.8611CAUGATPLINUT16ATPloop0.8611CAUGATPLINUT16ATPloop0.861<	c.3053C>T	p.A1018V	13	TM6/Ph	0.24	0	3
comparinginf<infinfinf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<inf<	c 3083A>G	p K1028R	14	Ph	0.08	0	1
Constructperformant1nout01Constructp100714n001constructp100714n0.8801constructp1018714ATP loop0.1610c1212C>Tp10181714ATP loop0.1611c1212C>Tp10181714ATP loop0.3411c1212C>Tp1018714ATP loop0.3411c1316A^Tp1018714ATP loop0.8801c135C>Tp1018714ATP loop0.8801c221C>Tp1018715ATP loop0.8801c231G>Ap1019715ATP loop0.8801c231G>Ap1019715ATP loop0.8801c231G>Ap1019715ATP loop0.8801c231G>Ap1192115ATP loop0.8801c231G>Ap1192115ATP loop0.8801c231G>Ap1192116ATP loop0.8801c231G>Ap1193116ATP loop0.8801c231G>Ap1193516ATP loop0.8801c231G>Ap1193516ATP loop0.8801c231G>Ap1193516ATP loop0.8801c231G>Ap119	c 3087dolT	p.C1030AfeY91	14	Ph	0.08	0	1
CAMAXAAPLUBATIAIPURUUUCAMAXAAPLUBATIAIP0.0801CAMAXAAPLUBATIAIP0.0801CAMAXAAPLUBATIAIP0.0810CAMAXAAPLUBATIAATIPIANO0.0810CAMAXAAPLUBATIAATIPIANO0.0801CAMAXAAPLUBATIAATIPIANO0.0801CAMAXAAPLUBATIAATIPIANO0.0801CAMAXAAPLUBATIAATIPIANO0.0801CAMAXAAPLUBATIAATIPIANO0.0801CAMAXAAPLUBATIAATIPIANO0.0801CAMAXAAPLUBATIAATIPIANO0.0801CAMAXAAPLUBATIAATIPIANO0.0801CAMAXAAPLUBATIAATIPIANO0.0801CAMAXAAPLUBATIAATIPIANO0.0801CAMAXAAPLUBATIAATIPIANO0.0801CAMAXAAPLUBATIAATIPIANO0.0801CAMAXAAPLUBATIAIAIA11CAMAXAAPLUBATIAIAIA11CAMAXAAPLUBATIAIAIA11CAMAXAAPLUBATIAIAIA <td>2000 C 1</td> <td>p.G1030AISA91</td> <td>14</td> <td></td> <td>0.00</td> <td>0</td> <td>1</td>	2000 C 1	p.G1030AISA91	14		0.00	0	1
CADD PACPITUD PACPA0.0801CADNECTPLTUD PAC14Ph0.0801CADNECTPLTUD PAC14ATT bop0.0801CADNECTPLTUD PAC14ATT bop0.0801CADNECTPLTUD PAC14ATT bop0.0801CADNECTPLTUD PAC14ATT bop0.0801CADNECTPLTUD PAC14ATT bop0.0801CADNECTPLTUD PAC15ATT bop0.0801CADNECTPLTUD PAC16ATT bop0.0801CADNECTPLTUD PAC16ATT bop0.0801CADNECTPLTUD PAC16ATT bop0.0801CADNECTPLTUD PAC16ATT bop0.0801CADNECTPLTUD PAC17ATT bop0.0801 <td>C.5069G-A</td> <td>p.GI050D</td> <td>14</td> <td>rn N</td> <td>0.40</td> <td>0</td> <td>5</td>	C.5069G-A	p.GI050D	14	rn N	0.40	0	5
C398C>Tp.T103114Ph0.0801C318C>Tp.C1085V14Ph0.0801C312C>Tp.K1081W14A.TPiloop0.1610C314CATp.1108V14A.TPiloop0.2411C315C>Tp.1108V14A.TPiloop0.0801C305CATp.1108V14A.TPiloop0.0801C305CTp.1108V14A.TPiloop0.0801C305TCp.1108V15A.TPiloop0.0801C305TCp.1108K15A.TPiloop0.0801C305TCp.1108K15A.TPiloop0.0801C305TCp.1112L15A.TPiloop0.0801C305CATp.1112L15A.TPiloop0.0801C305CATp.1112L15A.TPiloop0.8801C305CATp.1112L15A.TPiloop0.8801C305CATp.1112L16A.TPiloop0.8801C305CATp.1112L16A.TPiloop0.8801C305CATp.1113L16A.TPiloop0.8801C305CATp.1113K16A.TPiloop0.8801C305CAp.1113K16A.TPiloop0.8801C305CAp.1113K16A.TPiloop0.8801 </td <td>c.30951&gt;C</td> <td>p.110321</td> <td>14</td> <td>Ph</td> <td>0.08</td> <td>0</td> <td>1</td>	c.30951>C	p.110321	14	Ph	0.08	0	1
c.3003CPTp.0108V14N*n0.0801c.312CNCp.K0101V14A1Ploop0.6401c.312CNCp.10107V14A1Ploop0.6402c.316ANTp.10107V14A1Ploop0.6801c.316CNCp.10107V14A1Ploop0.8801c.320NCGp.10107K15A1Ploop0.8801c.321CNCp.10107K15A1Ploop0.8801c.321CNCp.10197K15A1Ploop0.8801c.331GNAp.11097K15A1Ploop0.8801c.331GNAp.111127KNG15A1Ploop0.8801c.331GNAp.111127KNG15A1Ploop0.8801c.343GNCp.111127KNG16A1Ploop0.8801c.3443CNCp.11137KNG16A1Ploop0.8801c.3443CNCp.11137KNG16A1Ploop0.8801c.3453CNGp.11137KNG16A1Ploop0.8801c.3453CNGp.11137KNG16A1Ploop0.8801c.3453CNGp.11137KNG16A1Ploop0.8801c.3453CNGp.11137KNG16A1Ploop0.8801c.3453CNGp.11137KNG16A1Ploop0.8801c.3553CNGp.1137KNG16	c.3098C>T	p.T1033I	14	Ph	0.08	0	1
c312C>Cp,R1011P14A TP loop0.1610c3140/A>Tp,R1011P14A TP loop0.4801c3140/A>TpP1057.14A TP loop0.1602c326C>CpP107R14A TP loop0.8801c326C>CpA107V14A TP loop0.8801c326C>CpA107V15A TP loop0.8801c326C>CpC1091R15A TP loop0.8801c376CApC101Y15A TP loop0.8801c331G>ApC101Y15A TP loop0.8801c331G>ApP112A15A TP loop0.8801c334G>CAp.1112A*/FX15A TP loop0.8801c343G>CAp.1112A*/FX16A TP loop0.8801c344G>CAp.1118T16A TP loop0.8801c444G>CAp.1118T16A TP loop0.8801c444G>CAp.1118T16A TP loop0.8801c453G>CAp.1117K16A TP loop0.8801c453G>CAp.1117K16A TP loop0.8801c453G>CAp.1117K16A TP loop0.8801c453G>CAp.1117K16A TP loop0.8801c453G>CAp.1117K16A TP loop <td>c.3104G&gt;T</td> <td>p.G1035V</td> <td>14</td> <td>Ph</td> <td>0.08</td> <td>0</td> <td>1</td>	c.3104G>T	p.G1035V	14	Ph	0.08	0	1
c.121C>Tp.D1047VIAAT loop0.840Ic.135C>Tp.D1047VIAAT loop0.8402c.135C>Tp.P1070RIAAT loop0.8501c.221C>Tp.L1088CIAT loop0.8201c.221C>Tp.L1088CIAT loop0.8201c.221A>Cp.L1088CIAT loop0.8601c.231G>Ap.T009PISAT loop0.8601c.331G>Ap.T1142FIAT loop0.8801c.331G>Ap.Y1184IAT loop0.8801c.331G>Ap.Y1184IAT loop0.8801c.331G>Ap.11147IAT loop0.8801c.343G>Cp.11147IAT loop0.8801c.344G>Ap.11147IAT loop0.8801c.344G>Ap.11148IAT loop0.8801c.345G>Ap.1117AIIAT loop0.8801c.355G>Ap.1117AIAT loop0.8601c.355G>Ap.1117AIAT loop0.8601c.355G>Ap.1117AIAT loop0.8601c.355G>Ap.1117AIAT loop0.8601c.355G>Ap.1117AIAT loop <td>c.3122G&gt;C</td> <td>p.R1041P</td> <td>14</td> <td>ATP loop</td> <td>0.16</td> <td>1</td> <td>0</td>	c.3122G>C	p.R1041P	14	ATP loop	0.16	1	0
chilabpH053/14ATPloop0.2411c1395C+pH07814ATPloop0.8601c2020C+pA1074V14ATPloop0.8801c2021C+pA1074V15ATPloop0.8801c2021C+pC1001R15ATPloop0.8801c2021A-CpT102215ATPloop0.8801c301G-ApT102415ATPloop0.8801c301G-ApV110415ATPloop0.8801c301G-ApV110415ATPloop0.8801c301G-ApV110415ATPloop0.8801c301G-ApV110416ATPloop0.8801c301G-CpV110416ATPloop0.8801c345C-TpV1134T16ATPloop0.8801c345C-TpV1134T16ATPloop0.8801c345C-GpV1134T16ATPloop0.8801c345C-GpV1134T16ATPloop0.8601c345C-GpV1134T16ATPloop0.8601c355C-GpV1134T16ATPloop0.8601c355C-GpV1134T17ATPloop0.8601c355C-GpV1134T16ATPloop0.8601c355C-GpV1	c.3121C>T	p.R1041W	14	ATP loop	0.08	0	1
chiSortpH00R14ATPloop0.6402c320C-CpH00R14ATPloop0.8401c321C-CpL108S15ATPloop0.8201c32TACpL108S15ATPloop0.8810c32TACpT109D15ATPloop0.8810c32TACpC104Y15ATPloop0.8801c3NiCAApY108A15ATPloop0.8801c3NiCAApY101A15ATPloop0.8801c3NiCAApY112X15ATPloop0.8801c3NiCAApQ1142H15ATPloop0.8801c3NiCAApQ1142H16ATPloop0.8801c3NiCAApQ1142H16ATPloop0.8801c340C-CpQ1142H16ATPloop0.8801c340C-CpX115C16ATPloop0.8801c345C-TpX115C16ATPloop0.8801c345C-TpX115C16ATPloop0.8601c352A-ACp117X16ATPloop0.8601c352A-ACp1178A16ATPloop0.8601c352A-ACp1178A16ATPloop0.8601c355C-ACp1178A16ATPloop0.8601c355C-ACp1178A	c.3140A>T	p.D1047V	14	ATP loop	0.24	1	1
accord c2221C>Tp.A1074Y14ATP hop0.0801c2221C>Tp.A1074Y14ATP hop0.0801c221T>Cp.L1088S15ATP hop0.0801c2271ACp.L108715ATP hop0.0801c231G>Ap.T1021*15ATP hop0.0801c331G>Ap.L1087*15ATP hop0.0801c331G>Ap.V1106115ATP hop0.0801c336C>Ap.V1106115ATP hop0.0801c336C>Cp.111231.15ATP hop0.0801c336C>Cp.11121416ATP hop0.0801c445C>Cp.11141*16ATP hop0.0801c445C>Cp.11141*16ATP hop0.0801c445C>Cp.11141*16ATP hop0.0801c445C>Cp.11181*16ATP hop0.0801c445C>Cp.11181*16ATP hop0.0801c455C>Cp.1117817ATP hop0.0801c455C>Cp.1117817ATP hop0.0801c455C>Cp.1117817ATP hop0.0801c455C>Cp.1117817ATP hop0.0801c455C>Cp.11281*17ATP hop0.080	c.3155C>T	p.P1052L	14	ATP loop	0.16	0	2
Construct         PAU07AY         14         ATH loop         0.08         0         1           CABGT>C         PAU07AY         14         ATH loop         0.08         0         1           CABGT>C         PLU08R         15         ATH loop         0.08         0         1           CAUATAC         PLU09R         15         ATH loop         0.08         0         1           CAUATAC         PLU02P         15         ATH loop         0.08         0         1           CAUATAC         PLU12A         15         ATH loop         0.08         0         1           CAUATAC         PLU12A         15         ATH loop         0.08         0         1           CAUATAC         PLU1AF         16         ATH loop         0.08	c 3209C>G	p P1070R	14	ATP loop	0.08	0	1
L2L1C1PL100YPL10PSPL10P	- 2001C>T	- A1074M	14	ATPlace	0.00	0	1
C.2.511-C.p.C.1091R.15A.11° loop0.3804C.22711-C.p.C.1091R.15A.TP loop0.0810C.231G-CA.p.C.1104Y.15A.TP loop0.0801C.331G-CA.p.J1123L.15A.TP loop0.0801C.337Sch4ACp.J1123L.15A.TP loop0.0801C.337Sch4ACp.J1123L.16A.TP loop0.8801C.337Sch4ACp.01421.16A.TP loop0.8801C.4345C>C.p.01421.16A.TP loop0.8801C.4465C>A.p.01421.16A.TP loop0.8801C.4465C>A.p.K1131.16A.TP loop0.8801C.451C>G.p.K1131.16A.TP loop0.8801C.455C>A.p.K1131.16A.TP loop0.8801C.455C>A.p.K1137.16A.TP loop0.8801C.455C>A.p.K1137.16A.TP loop0.8801C.455C>A.p.K1137.16A.TP loop0.8801C.455C>A.p.K1137.16A.TP loop0.8801C.455C>A.p.K1137.16A.TP loop0.8801C.555C>A.p.K1137.17A.TP loop0.8801C.555C>A.p.K1137.18A.TP loop0.8811<		p.A10/4V	14	ATP100p	0.08	0	1
C221PCCp.TL09/R15A.TP loop0.0801C321ACCp.TL01Y15A.TP loop0.0801C31GCAp.V110415A.TP loop0.0801C33GCAp.V110415A.TP loop0.0801C33GCAp.H1124Flv3C15A.TP loop0.0801C33GCAp.H1124Flv3C15A.TP loop0.8801C33GCAp.G114Flv316A.TP loop0.8801C34GCACp.G114Flv316A.TP loop0.8801C34GCACp.G114Flv316A.TP loop0.8801C34GCACp.R1151G16A.TP loop0.8601C45GCACp.R1151H16A.TP loop0.8801C45GCACp.R1151K16A.TP loop0.8801C45GCACp.R1151K16A.TP loop0.8801C45GCACp.D119KC17A.TP loop0.8801C45GCACp.D119KC17A.TP loop0.8801C45GCACp.V120KH17A.TP loop0.8801C45GCACp.V120KH17A.TP loop0.8801C45GCACp.V120KH18A.TP loop0.8801C45GCACp.V120KH18A.TP loop0.8801C45GCACp.V120KH18A.TP	c.32631>C	p.L10885	15	ATPloop	0.32	0	4
c3274ACp.T1092P15ATP kop0.0810c331GCAp.C1104Y15ATP kop0.0801c336CGAp.P112L15ATP kop0.0801c337GALACp.P112L15ATP kop0.0801c337GALACp.P112L16ATP kop0.0801c337GALACp.114F116ATP kop0.0801c348GCp.114F116ATP kop0.0801c344GCAp.114F116ATP kop0.0801c344GCAp.R115IG16ATP kop0.0801c345ICAp.R115IG16ATP kop0.0801c345CAp.R115IG16ATP kop0.0801c35GACp.R115IG16ATP kop0.0801c35GACp.R115R16ATP kop0.0801c35GACp.T178A16ATP kop0.0801c35GACp.1115R17ATP kop0.0801c35GACp.1115R17ATP kop0.0801c35GACp.1115R17ATP kop0.0801c35GACp.1128P17ATP kop0.0801c35GACp.1128P17ATP kop0.0801c35GACp.1128P18ATP kop0.0801c35GAC <td>c.3271T&gt;C</td> <td>p.C1091R</td> <td>15</td> <td>ATP loop</td> <td>0.08</td> <td>0</td> <td>1</td>	c.3271T>C	p.C1091R	15	ATP loop	0.08	0	1
c331GCAp.C110Y15ATP loop1.0801C336GCAp.V1106115ATP loop1.08012C336GCAp.P1122L15ATP loop0.0801C337GS735R6IACp.P1124C15ATP loop0.0801C342GCCp.Q114GT16ATP loop3.22140C344GCAp.G110F16ATP loop0.0801C34GCAp.R115IC16ATP loop0.0801C45GCCAp.R115IC16ATP loop0.0801C45GCAp.R115IC16ATP loop0.0801C45GCAp.R115IC16ATP loop0.0801C45GCAp.R1173K16ATP loop0.0801C35GCAp.L1173K16ATP loop0.0801C35GCAp.L118R17ATP loop0.0801C35GCAp.1118A17ATP loop0.0801C35GCAp.1128F17ATP loop0.0801C35GCAp.1128F17ATP loop0.0801C35GCAp.1128F17ATP loop0.0801C35GCAp.1128F18ATP loop0.0801C35GCAp.1128F18ATP loop0.0801C35GCAp.1128F18ATP loop0.0801 </td <td>c.3274A&gt;C</td> <td>p.T1092P</td> <td>15</td> <td>ATP loop</td> <td>0.08</td> <td>1</td> <td>0</td>	c.3274A>C	p.T1092P	15	ATP loop	0.08	1	0
c331GC>ApyTh10d15ATP loop1.03013c336C-7p/11120FxX15ATP loop0.0801c33723AdLACp.01142H16ATP loop0.0801c342GC-Cp.01142H16ATP loop3.22140c344GC-Ap.C1149E16ATP loop0.0801c344GC-Ap.R1151C16ATP loop0.0801c3451C-Tp.R1151H16ATP loop0.1602c3450C-Tp.R1151H16ATP loop0.1602c353CACp.R117XK16ATP loop0.1602c353CACp.117XA16ATP loop0.1601c353CA-Gp.1118R17ATP loop0.1801c353CA-Gp.1118R17ATP loop0.8801c353CA-Gp.1118R17ATP loop0.8801c353CA-Gp.1118R17ATP loop0.8801c353CA-Gp.1118R17ATP loop0.8801c353CA-Gp.11245A18ATP lond0.8201c353CA-Gp.11245A18ATP lond0.8801c353CA-Gp.11245A18ATP lond0.8801c353CA-Gp.11245A18ATP long0.8801c353CA-Gp.11245A18ATP long <td>c.3311G&gt;A</td> <td>p.C1104Y</td> <td>15</td> <td>ATP loop</td> <td>0.08</td> <td>0</td> <td>1</td>	c.3311G>A	p.C1104Y	15	ATP loop	0.08	0	1
c338C7Tp1121.i5ATP loop0.0801c3377_337delACp11148716ATP loop1.58118c3426C-CpQ1142H16ATP loop3.52140c343C5ACpC1149E16ATP loop0.8801c345C-CpR115G16ATP loop0.8801c345C-CApR115G16ATP loop0.8801c345C-CApR115G16ATP loop0.8801c345C-CApR115G16ATP loop0.8801c355C3C-CApR115R16ATP loop0.8801c355C3C-GpL1178A16ATP loop0.8801c355C3C-GpL1188R17ATP loop0.8801c365CC-GpL118P17ATP loop0.8801c365CC-GpL128P17ATP loop0.8801c365CC-GpL128P17ATP loop0.8801c375CC-GpL128P18ATP lond0.8801c375CC-GpL128P18ATP lond0.8801c375CC-GpL128P18ATP long0.8811c375CC-GpL128P18ATP long0.8801c375CC-GpL128P18ATP long0.8801c375CC-GpL128F18ATP long0.881 <td>c.3316G&gt;A</td> <td>p.V1106I</td> <td>15</td> <td>ATP loop</td> <td>1.03</td> <td>0</td> <td>13</td>	c.3316G>A	p.V1106I	15	ATP loop	1.03	0	13
c.337.33kelACp.11126/5X315ATP loop0.0801c.3426CCp.01142H16ATP loop3.22140c.344GCAp.01142H16ATP loop0.8801c.344GCAp.0115C16ATP loop0.8801c.345ICCTp.N115G16ATP loop0.8801c.345ICCTp.N115G16ATP loop0.8801c.345ICCTp.N115C16ATP loop0.8801c.345ICCTp.N115C16ATP loop0.8801c.353ICCAp.11178A16ATP loop0.8801c.353ICCAp.11178A16ATP loop0.8801c.353ICCAp.1118R17ATP loop0.8801c.363ICCAp.11216M17ATP loop0.8801c.363ICCAp.11216M17ATP loop0.8801c.363ICCAp.11244N18ATP lond0.8801c.363ICCAp.11244N18ATP lond0.8801c.363ICCAp.11244N18ATP lond0.8801c.363ICCAp.11244N18ATP lond0.8801c.371GCAp.1124A18ATP long0.8601c.371GCAp.1124A18ATP long0.8601c.371GCAp.1124A18	c.3368C>T	p.P1123L	15	ATP loop	0.08	0	1
add         pQ1142H         16         ATP loop         158         1         18           c344G>C         pG1148T         16         ATP loop         3.32         1         40           c344G>A         pG1149F         16         ATP loop         0.8         0         1           c345IC>T         pR115IC         16         ATP loop         0.8         0         1           c345C>A         pR115IG         16         ATP loop         0.8         0         1           c345C>A         pR115IK         16         ATP loop         0.8         0         1           c353C>A         pL1173K         16         ATP loop         0.8         0         1           c353CA         pL1178K         16         ATP loop         0.8         0         1           c353CA         pL118R         17         ATP loop         0.8         0         1           c353CAC         pL118R         17         ATP loop         0.8         0         1           c353GCC         pL128P         17         ATP loop         0.8         0         1           c354GCA         p.V122M         18         ATP lond         0.8         <	c.3377_3378delAC	p.H1126PfsX3	15	ATP loop	0.08	0	1
CAMODPALINA	c 3426G>C	n O1142H	16	ATP loop	1 58	1	18
Cambredpintering <t< td=""><td>2442T&gt;C</td><td>p.Q111211</td><td>16</td><td>ATPlaan</td><td>2.22</td><td>1</td><td>10</td></t<>	2442T>C	p.Q111211	16	ATPlaan	2.22	1	10
CAMBRCYARDATAFANCEDATAFANCEDATAFANCEDATAFANCEDATAFANCECAMBRCYARPRIDIC16ATP loop0.0801CASEICCGPRIDIG16ATP loop0.0801CASECCAPRIDISH16ATP loop0.0801CASECCAPRIDISK16ATP loop0.0801CASECCAPLITAK16ATP loop0.0801CASECCAPLITAK16ATP loop0.0801CASECCAPLITAK16ATP loop0.0801CASECCAPLITAK17ATP loop0.0801CASECCAPLIDAGC17ATP loop0.0801CASECCAPLIDAGC17ATP loop0.0801CASECCAPLIDAGC17ATP loop0.0801CASECCAPLIDAGC17ATP loop0.0801CASECCAPLIDAGC17ATP loop0.0801CASECCAPLIDAGC18ATP lind0.0801CASECCAPLIDAGC18ATP lind0.0801CASECCAPLIDAGC18ATP ling0.0801CASECCAPLIDAGC18ATP ling0.0801CASECCAPLIDAGC18ATP ling0.0801CASECCAPLIDAGC18ATP ling0.080<	- 244/05 4	p.111461	16	ATPLOOP	0.00	1	40
C4B1C>IpARI 51C16A TP koop0.0801C4B1C>CpRI 151G16A TP koop0.6602C4B2C>ApRI 151H16A TP koop0.0801C4B2C>ApRI 157K16A TP koop0.0801C557CApT1 178A16A TP koop0.0602C557CApT1 178A16A TP koop0.0801C557CApL1 188R17A TP koop0.0801C5587CApL1 188R17A TP koop0.0801C3687CApL1 188R17A TP koop0.0801C3687CApL1 218P17A TP koop0.0801C3687CApL1 218P17A TP koop0.0801C3687CApL1 218P17A TP kind0.8801C371CCpL1 218P17A TP kind0.8801C373CCGpL1 228F18A TP kind0.8801C374CApC1 29V18A TP kind0.8801C376CATpL2 56Fx/5718A TP king0.0801C376CATpL2 56Fx/5718A TP king0.8801C376CATpL2 56Fx/5718A TP king0.8801C380CAApL1279C18A TP king0.8801C380CAApL1279C18A TP king	C.3446G>A	p.GI149E	16	ATP loop	0.08	0	1
CABIC>Gp.R1151G16ATP loop0.0801CABCC>Ap.K1151H16ATP loop0.1602CABSC>Ap.E1173K16ATP loop0.7918CASTC>Ap.E1173K16ATP loop0.1602CASTC>Ap.E1173K16ATP loop0.1602CASTC>Ap.1118A17ATP loop0.0801CASTC>Ap.1118K17ATP loop0.0801CASTC>CAp.1118K17ATP loop0.0801CASTC>CAp.1120G17ATP loop0.0801CAGCC>CAp.11218N17ATP loop0.0801CAGCC>CAp.11218N17ATP loop0.0801CAGCC>CAp.11218N17ATP lond0.3204CASTC>CAp.11218N18ATP bind0.3201CAGCC>CAp.1124K18ATP bind0.8801CASTC>CAp.1124Q18ATP bind0.8801CASTC>CAp.1124Q18ATP bind0.8801CASTC>CAp.1124Q18ATP linge0.8801CASTC>CAp.1124Q18ATP linge0.8801CASTC>CAp.1124Q18ATP linge0.8801CASTC>CAp.1124G18ATP linge0.88 </td <td>c.3451C&gt;1</td> <td>p.R1151C</td> <td>16</td> <td>ATP loop</td> <td>0.08</td> <td>0</td> <td>1</td>	c.3451C>1	p.R1151C	16	ATP loop	0.08	0	1
c.3452C>Ap.R1151H16ATP loop0.1602c.3459C>Ap.W1135C16ATP loop0.0801c.3557LAp.E1173K16ATP loop0.7918c.3552LACp.T1178A16ATP loop0.0801c.3557LAp.D1196C17ATP loop0.0801c.3557LAp.D1196C17ATP loop0.0801c.3567LACp.D1196C17ATP loop0.0801c.366CCGp.J1202C17ATP loop0.0801c.366CCAp.V1216M17ATP loop0.0801c.366CCAp.V1216NC18ATP lond0.9204c.370104Gp.V1224L5X9C18ATP lond0.8801c.3732CGp.P1245A18ATP lond0.8801c.3776CTp.01250FX5718ATP lind0.8801c.3776CTp.01250FX5718ATP ling0.8801c.3776CTp.01250FX5718ATP ling0.8801c.3802CSAp.01250FX5718ATP ling0.8801c.3802CSAp.01250F18ATP ling0.8801c.3802CSAp.01270C18ATP ling0.8801c.3804CTp.1273L18ATP ling0.8801c.3805CAp.1298F<	c.3451C>G	p.R1151G	16	ATP loop	0.08	0	1
c3480C>TpMU153C16ATP loop0.0801c3517C>ApE1173K16ATP loop0.7918c3552A>Cp1178A16ATP loop0.0801c3557A>asyna7ATP loop0.0801c3563T>Cp.1118R17ATP loop0.0801c3563T>Cp.1120C17ATP loop0.0801c366C>Cp.V120K17ATP loop0.0801c366C>Cp.V1216M17ATP loop0.0801c360C>Cp.V123K18ATP bind0.0801c3705CATp.V123F18ATP bind0.0801c3715CATp.V123F18ATP bind0.0801c3715CATp.V123F18ATP bind0.0801c3715CATp.V123F18ATP bind0.0801c3765ArdupCAp.Q125F16X7518ATP hing0.0801c3765ArdupCAp.G125V18ATP hing0.801c3802A>Cp.N127S18ATP hing0.801c3804Ap.N127S18ATP hing0.801c3804Ap.N127S18ATP hing0.801c3818CATp.N127S18ATP hing0.801c3818CATp.N128SK18ATP hing0.80<	c.3452G>A	p.R1151H	16	ATP loop	0.16	0	2
c3512p.H173K16ATP loop0.7918c3532p.H178A16ATP loop0.1602c3557p.A17ATP loop0.8801c3567p.H188R17ATP loop0.8801c3587p.M196G17ATP loop0.8801c3567p.M203G17ATP loop0.8801c3665p.M203G17ATP loop0.8801c3665p.M204G17ATP loid0.8801c3665p.M204G18ATP loid0.8801c3704Gp.V124L5X9618ATP loid0.8801c3731CSCTp.M128F18ATP loid0.8801c3741CSGp.M124G18ATP loid0.8801c376CATp.G1259Y18ATP loing0.8801c376CATp.M124GT18ATP loing0.8801c3802AGp.G1258Y18ATP loing0.8801c3802AGp.M126T18ATP loing0.8801c3804AGp.M127G18ATP loing0.8801c3804AGp.M127G18ATP loing0.8401c3804AGp.M128Y18ATP loing0.8401c3805AGp.M128Y18ATP loing0.8401 <tr< td=""><td>c.3459G&gt;T</td><td>p.W1153C</td><td>16</td><td>ATP loop</td><td>0.08</td><td>0</td><td>1</td></tr<>	c.3459G>T	p.W1153C	16	ATP loop	0.08	0	1
c.3332AGp.T1178A16ATP loop0.1602c.35572A2%na17ATP loop0.0801c.35637AGp.D1196G17ATP loop0.0801c.3605CGp.A1202G17ATP loop0.0801c.3605CAGp.V1216M17ATP bind1.98221c.3605CAGp.V1214L5X9618ATP bind0.2204c.3705CAGp.V1234L5X9618ATP bind0.2204c.3703CGp.V1234L5X9618ATP bind0.0801c.3733CCGp.V1234L5X9618ATP bind0.0801c.374CAGp.V1234C18ATP bind0.0801c.376GA1QCAp.Q1256P5X7518ATP bind0.0801c.376GA1QCAp.Q1256P5X7518ATP hinge0.0801c.3902AGp.N1270518ATP hinge0.0801c.3802AAp.N1270518ATP hinge0.0801c.3802AAp.N1270518ATP hinge0.0801c.3805ACp.D1279G18ATP hinge0.0801c.3805ACAp.D1279G18ATP hinge0.0801c.3805ACAp.D1279G18ATP hinge0.0801c.3805ACAp.D1295V18ATP hinge0.0801c.3805CA <td>c.3517G&gt;A</td> <td>p.E1173K</td> <td>16</td> <td>ATP loop</td> <td>0.79</td> <td>1</td> <td>8</td>	c.3517G>A	p.E1173K	16	ATP loop	0.79	1	8
c.3557-2a>g       na       17       ATP loop       0.08       0       1         c.3567-SG       p.L1188R       17       ATP loop       0.08       0       1         c.3567-SG       p.D1196G       17       ATP loop       0.08       0       1         c.3605-CG       p.A1202G       17       ATP loop       0.08       0       1         c.3646CA       p.V1216M       17       ATP lood       0.08       0       1         c.370304G       p.V1234L6X96       18       ATP bind       0.32       0       4         c.370305G       p.P1245A       18       ATP bind       0.08       0       1         c.3714C-G       p.Q1256PfSX75       18       ATP bind       0.08       0       1         c.3765.3767dupCA       p.Q1256PfSX75       18       ATP bind       0.08       0       1         c.3705C-T       p.Q1256PfSX75       18       ATP hinge       0.08       0       1         c.3706C3T       p.Q1256PfSX75       18       ATP hinge       0.8       0       1         c.3707CA       p.G1259V       18       ATP hinge       0.8       0       1         c.3802CA       <	c.3532A>G	p.T1178A	16	ATP loop	0.16	0	2
Cases of the second s	c 3557-2a>g	na	17	ATP loop	0.08	0	1
Labort O         PATROX         PATRO	c 3563T>G	n I 1188R	17	ATP loop	0.08	0	1
CLBDF/AC         PL1796C         P         ATI bop         0.08         0         1           C3605C         p.A1202G         17         ATP bord         0.08         0         1           c3646C>A         p.V1216M         17         ATP bind         0.08         0         1           c3635TC         p.L1218P         17         ATP bind         0.02         0         4           c3700delG         p.V1234LfsX96         18         ATP bind         0.24         0         3           c3735C5         p.V1234F         18         ATP bind         0.08         0         1           c3761/CG         p.H1247Q         18         ATP bind         0.08         0         1           c3764.0pCA         p.Q1256/FsX75         18         ATP hinge         0.08         0         1           c3763.0pCA         p.Q1256/FsX75         18         ATP hinge         0.08         0         1           c3763.0pCA         p.Q1256/FsX75         18         ATP hinge         0.08         0         1           c3760.0pCA         p.Q1256/FsX75         18         ATP hinge         0.08         0         1           c3804DC         p.N12705	25071×G	p.E1106K	17	ATRicon	0.08	0	1
C-800-CG         p.A120AC         P         ATP loop         0.08         0         1           c.364GCA         p.V1216M         17         ATP bind         0.08         0         1           c.363TPC         p.L1218P         17         ATP bind         0.32         0         4           c.3701GC         p.V1234Lf.5x96         18         ATP bind         0.24         0         3           c.3713CG         p.V1239F         18         ATP bind         0.08         0         1           c.3734CCG         p.P1245A         18         ATP bind         0.08         0         1           c.3766_3767dupCA         p.Q1256Pf5X75         18         ATP hinge         0.08         0         1           c.3760F1         p.G1258V         18         ATP hinge         0.08         0         1           c.3802G>A         p.G1268R         18         ATP hinge         0.08         0         1           c.3802G>A         p.P1273L         18         ATP hinge         0.08         0         1           c.3804AC         p.P1273Q         18         ATP hinge         0.24         0         3           c.3818CA         p.L128X <td< td=""><td>C.556/A2G</td><td>p.D1198G</td><td>17</td><td>ATPloop</td><td>0.08</td><td>0</td><td>1</td></td<>	C.556/A2G	p.D1198G	17	ATPloop	0.08	0	1
c.364G>Ap.V1216M17A TP bind1.98221c.3653T>Cp.L1218P17A TP bind0.0801c.3701deIGp.V1234LfsX9618A TP bind0.3204c.3733C>Gp.V1239F18A TP bind0.0801c.3733C>Gp.P1245A18A TP bind0.0801c.3736_3T>Gp.P1245A18A TP bind0.0801c.3766_3767dupCAp.Q1256PfsX7518A TP bind0.0801c.3766_3767dupCAp.Q1256PfsX7518A TP hinge0.0801c.3791T>Cp.M1264T18A TP hinge0.0801c.3802A>Ap.G1268R18A TP hinge0.0801c.3803A>Gp.N1270S18A TP hinge0.0801c.3818C>Tp.P1273L18A TP hinge0.0801c.3848C>Tp.D1279G18A TP hinge0.0801c.3848C>Tp.A1283V18A TP hinge0.0801c.3848C>Tp.A1293K18A TP hinge0.0801c.3846C>Tp.A1283V18A TP hinge/TM70.0801c.3846C>Tp.A1293K18A TP hinge/TM70.0801c.3846C>Tp.A1293K18A TP hinge/TM70.0801c.3846C>Tp.A1293K18A TP hinge/TM7 <t< td=""><td>c.3605C&gt;G</td><td>p.A1202G</td><td>17</td><td>ATPloop</td><td>0.08</td><td>0</td><td>1</td></t<>	c.3605C>G	p.A1202G	17	ATPloop	0.08	0	1
c.3637PCp.L1218P17ATP bind0.0801c.3700delGp.V1234Lfx59618ATP bind0.3204c.3715G-Tp.V123PF18ATP bind0.0801c.3741C>Gp.P1245A18ATP bind0.0801c.376G.3767dupCAp.Q1256Pfx7518ATP bind0.0801c.376G.3767dupCAp.Q1256Pfx7518ATP binge0.0801c.376G.57p.Q1256Pfx7518ATP binge0.0801c.3791P-Cp.M1264T18ATP binge0.0801c.3802C>Ap.N1270S18ATP binge0.0801c.3808C>Ap.N1270S18ATP binge0.0801c.3818C>Tp.P1273L18ATP binge0.0801c.3836A>Gp.D1279G18ATP binge0.0801c.3848C>Tp.A1283V18ATP binge0.0801c.3848C>Tp.A1283V18ATP binge0.0801c.3867G>Ap.E1293K18ATP binge/TM70.4005c.3867G>Ap.A129SV18ATP binge/TM70.0801c.3904.5gsap.A129SV18ATP binge/TM70.0801c.3905.5psana18ATP binge/TM70.0801c.3905.5psana18ATP binge/TM70.060 <td>c.3646G&gt;A</td> <td>p.V1216M</td> <td>17</td> <td>ATP bind</td> <td>1.98</td> <td>2</td> <td>21</td>	c.3646G>A	p.V1216M	17	ATP bind	1.98	2	21
c.370delGp.V1234LfsX9618ATP bind0.3204c.371GCATp.V1239F18ATP bind0.2403c.3733CCGp.P1245A18ATP bind0.0801c.3741CCGp.H1247Q18ATP bind0.0801c.3766_3767dupCAp.Q1256PfsX7518ATP bing0.0801c.3776C>Tp.G1259V18ATP hinge0.0801c.3701CCp.G1258V18ATP hinge0.0801c.3802CAp.G1268R18ATP hinge0.0801c.3804CAp.D1270518ATP hinge0.0801c.3804CAp.D1270518ATP hinge0.0801c.3818C>Tp.P1273L18ATP hinge0.0801c.3848C>Tp.D1279G18ATP hinge0.0801c.3848C>Tp.A1283V18ATP hinge0.0801c.3897C>Ap.A1283V18ATP hinge0.0801c.3896T>Gp.A129SV18ATP hinge/TM70.4005c.3896T>Gp.A129SV18ATP hinge/TM70.0801c.3901_S02Ap.R1301KfsX318ATP hinge/TM70.0801c.3904Tp.A129SV18ATP hinge/TM70.0801c.3904Tp.A129F18ATP hinge/TM70.0801	c.3653T>C	p.L1218P	17	ATP bind	0.08	0	1
c.3715G>Tp.V1239F18ATP bind0.2403c.3733C>Gp.P1245A18ATP bind0.0801c.3741C>Gp.P1256PfsX7518ATP bind0.0801c.3766/376/upCAp.Q1256PfsX7518ATP bind0.0801c.3766/37Cp.G1259V18ATP hinge0.0801c.3705C>Tp.G1256PfsX7518ATP hinge0.0801c.3802C>Ap.M1264T18ATP hinge0.0801c.3803C>Ap.N1270S18ATP hinge0.0801c.3804SCp.N1270S18ATP hinge0.0801c.3818C>Ap.P1273L18ATP hinge0.1602c.3818C>Ap.N1270S18ATP hinge0.1602c.3848C>Tp.N128Y18ATP hinge0.0801c.3848C>Tp.A1285Y18ATP hinge0.0801c.3896T>Gp.A1285Y18ATP hinge/TM70.4005c.3896T>Gp.R1301KfsX318ATP hinge/TM70.0801c.3903-652>1p.R1301KfsX319ATP hinge/TM70.0801c.3905C>Tp.R1319X19TM70.1602c.4005GACp.G1335mLJWVA19TM70.1603	c.3700delG	p.V1234LfsX96	18	ATP bind	0.32	0	4
c.3733C>Gp.P1245A18ATP bind0.0801c.3741C>Gp.H1247Q18ATP bind0.0801c.37663Tp.Q1256PfsX7518ATP bind0.0801c.3776C>Tp.M1264T18ATP hinge0.0811c.3802C>Ap.G1258PfsX7518ATP hinge0.0801c.3802C>Ap.M1264T18ATP hinge0.0801c.3803C>Ap.G1268R18ATP hinge0.0801c.3818C>Tp.P1273L18ATP hinge0.0801c.3818C>Ap.P1273Q18ATP hinge0.1602c.3848C>Tp.P1273Q18ATP hinge0.0801c.3848C>Tp.A1283V18ATP hinge0.0801c.3848C>Tp.G1287S18ATP hinge0.0801c.3848C>Tp.A1293V18ATP hinge0.0801c.3848C>Tp.A1295V18ATP hinge/TM70.4005c.39015Ap.R1293K18ATP hinge/TM70.0801c.39015Ap.R1301KfsX318ATP hinge/TM70.0801c.3903+5g>ana18ATP hinge/TM70.0801c.3903+5g>ap.R1319X19TM70.1602c.4003G>Cp.G1335insLWWA19TM70.1602	c.3715G>T	p.V1239F	18	ATP bind	0.24	0	3
c.3741C>G       p.H1247Q       18       ATP bind       0.08       0       1         c.3766_3767dupCA       p.Q1256PfsX75       18       ATP bind       0.08       0       1         c.3776C>T       p.G1259V       18       ATP hinge       0.08       1       1         c.3791T>C       p.G1256R       18       ATP hinge       0.08       0       1         c.3802C>A       p.G1266R       18       ATP hinge       0.08       0       1         c.3804AC       p.N1270S       18       ATP hinge       0.08       0       1         c.3818C>A       p.N1270S       18       ATP hinge       0.08       0       1         c.3818C>A       p.P1273L       18       ATP hinge       0.06       0       2         c.3848C>T       p.1279G       18       ATP hinge       0.08       0       1         c.3897G>A       p.G1287S       18       ATP hinge       0.08       0       1         c.3896C>G       p.G129K       18       ATP hinge/TM7       0.40       0       5         c.3896C>G       p.1129R       18       ATP hinge/TM7       0.08       0       1         c.3901_3902insA	c.3733C>G	p.P1245A	18	ATP bind	0.08	0	1
c.3766_J767dupCA       p.Q1256PfsX75       18       ATP bind       0.08       0       1         c.3776G>T       p.G1259PfsX75       18       ATP hinge       0.08       1       1         c.3776G>T       p.G1258PfsX75       18       ATP hinge       0.08       0       1         c.3701T>C       p.M1264T       18       ATP hinge       0.08       0       1         c.3802C>A       p.G1268R       18       ATP hinge       0.08       0       1         c.3802C>A       p.M1270S       18       ATP hinge       0.08       0       1         c.3818C>T       p.P1273L       18       ATP hinge       0.08       0       1         c.3818C>A       p.P1273Q       18       ATP hinge       0.08       0       1         c.3818C>A       p.D1279G       18       ATP hinge       0.08       0       1         c.3848C>T       p.A1283V       18       ATP hinge       0.08       0       1         c.3848C>T       p.A1295V       18       ATP hinge       0.08       0       1         c.3848C>T       p.A1295V       18       ATP hinge/TM7       0.40       0       3         c.3896T>G<	c.3741C>G	p.H1247O	18	ATP bind	0.08	0	1
C.5.05 of unper 1         p.G1250V         18         ATP binder         0.08         1         1           c.377GC>T         p.G1259V         18         ATP hinge         0.08         0         1           c.3791T>C         p.M1264T         18         ATP hinge         0.08         0         1           c.3802C>A         p.G1268R         18         ATP hinge         0.08         0         1           c.3803A>G         p.N1270S         18         ATP hinge         0.08         0         1           c.3818C>T         p.P1273L         18         ATP hinge         0.08         0         1           c.3818C>A         p.P1273Q         18         ATP hinge         0.08         0         1           c.3818C>A         p.D1279G         18         ATP hinge         0.08         0         1           c.3848C>T         p.A1283V         18         ATP hinge         0.08         0         1           c.3876C>A         p.E1293K         18         ATP hinge         0.08         0         1           c.3876C>A         p.E1293K         18         ATP hinge/TM7         0.40         0         5           c.38901_902insA         p.R1301K	c 3766_3767dupC A	n O1256PfeX75	18	ATP bind	0.08	0	1
C.S.YAC-1         p.C.12.9V         18         A.TP. Image         0.08         1         1           c.3791T>C         p.M1264T         18         A.TP. Image         0.08         0         1           c.38025-A         p.G1268R         18         A.TP. Image         0.08         0         1           c.3809A>G         p.N1270S         18         A.TP. Image         0.08         0         1           c.3818C>T         p.P1273L         18         A.TP. Image         0.08         0         1           c.3818C>A         p.P1273Q         18         A.TP. Image         0.08         0         1           c.3884c>T         p.A1283V         18         A.TP. Image         0.08         0         1           c.3884c>T         p.G1287S         18         A.TP. Image         0.08         0         1           c.3884c>T         p.G1293K         18         A.TP. Image         0.08         0         1           c.3884c>T         p.A1295V         18         A.TP. Image         0.40         0         5           c.38901_3002insA         p.R1301KfsX3         18         A.TP. Image/TM7         0.40         0         1           c.3903+5g>a	-277(C>T	p.Q1250113/075	10	ATD his se	0.00	1	1
c.3/911>C       p.M12641       18       ATP hinge       0.08       0       1         c.3802>A       p.G1268R       18       ATP hinge       0.08       0       1         c.3809A>G       p.N1270S       18       ATP hinge       0.08       0       1         c.3818C>T       p.P1273L       18       ATP hinge       0.08       0       1         c.3818C>A       p.P1273Q       18       ATP hinge       0.24       0       3         c.3848C>T       p.A1283V       18       ATP hinge       0.08       0       1         c.3848C>T       p.G1287S       18       ATP hinge       0.08       0       1         c.3884C>T       p.G1287S       18       ATP hinge       0.08       0       1         c.3884C>T       p.G1287S       18       ATP hinge       0.08       0       1         c.3884C>T       p.G1293K       18       ATP hinge/TM7       0.40       0       5         c.3896T>G       p.L1299R       18       ATP hinge/TM7       0.08       0       1         c.3901_3902insA       p.R1301KfsX3       18       ATP hinge/TM7       0.08       0       1         c.3903+5g>a <td>C.3776G21</td> <td>p.G1259V</td> <td>18</td> <td>ATPhinge</td> <td>0.08</td> <td>1</td> <td>1</td>	C.3776G21	p.G1259V	18	ATPhinge	0.08	1	1
c.3802G>A       p.G1268R       18       A IP hinge       0.08       0       1         c.3809A>G       p.N1270S       18       A TP hinge       2.22       0       28         c.3818C>T       p.P1273L       18       A TP hinge       0.08       0       1         c.3818C>A       p.P1273Q       18       A TP hinge       0.16       0       2         c.3836A>G       p.D1279G       18       A TP hinge       0.24       0       3         c.3848C>T       p.A1283V       18       A TP hinge       0.08       0       1         c.3859G>A       p.G1287S       18       A TP hinge       0.08       0       1         c.387G>A       p.E1293K       18       A TP hinge       0.08       0       1         c.387G>A       p.E1293K       18       A TP hinge/TM7       0.40       0       5         c.3896T>G       p.A1295V       18       A TP hinge/TM7       0.08       0       1         c.3901_3902insA       p.R1301KfsX3       18       A TP hinge/TM7       0.08       0       1         c.3995C>T       p.R1319X       19       A TP hinge/TM7       0.08       0       3 <t< td=""><td>c.37911&gt;C</td><td>p.M12641</td><td>18</td><td>AIPhinge</td><td>0.08</td><td>0</td><td>1</td></t<>	c.37911>C	p.M12641	18	AIPhinge	0.08	0	1
c.3809A>G       p.N1270S       18       ATP hinge       2.22       0       28         c.3818C>T       p.P1273L       18       ATP hinge       0.08       0       1         c.3818C>A       p.P1273Q       18       ATP hinge       0.16       0       2         c.3836A>G       p.D1279G       18       ATP hinge       0.24       0       3         c.3848C>T       p.A1283V       18       ATP hinge       0.08       0       1         c.3859G>A       p.G1287S       18       ATP hinge       0.08       0       1         c.3877G>A       p.G1287S       18       ATP hinge       0.08       0       1         c.3884C>T       p.A1293K       18       ATP hinge       0.08       0       1         c.3897G>A       p.B1293K       18       ATP hinge/TM7       0.40       0       5         c.3896T>G       p.L1299R       18       ATP hinge/TM7       0.08       0       1         c.3901_3902insA       p.R1301KfsX3       18       ATP hinge/TM7       0.08       0       1         c.3903+5g>a       na       18       ATP hinge/TM7       0.08       0       3         c.3982G>A <td>c.3802G&gt;A</td> <td>p.G1268R</td> <td>18</td> <td>ATP hinge</td> <td>0.08</td> <td>0</td> <td>1</td>	c.3802G>A	p.G1268R	18	ATP hinge	0.08	0	1
c.3818C>T       p.P1273L       18       ATP hinge       0.08       0       1         c.3818C>A       p.P1273Q       18       ATP hinge       0.16       0       2         c.3836A>G       p.D1279G       18       ATP hinge       0.24       0       3         c.3848C>T       p.A1283V       18       ATP hinge       0.08       0       1         c.3859G>A       p.G1287S       18       ATP hinge       0.08       0       1         c.3877G>A       p.E1293K       18       ATP hinge       0.08       0       1         c.3897S>A       p.A1283V       18       ATP hinge       0.08       0       1         c.3877G>A       p.E1293K       18       ATP hinge/TM7       0.40       0       5         c.3896T>G       p.I1299R       18       ATP hinge/TM7       0.08       0       1         c.3901_3902insA       p.R1301KfsX3       18       ATP hinge/TM7       0.08       0       1         c.3995T>CT       na       18       ATP hinge/TM7       0.08       0       1         c.3995TSC>T       na       18       ATP hinge/TM7       0.08       0       3         c.3982C>A	c.3809A>G	p.N1270S	18	ATP hinge	2.22	0	28
c.3818C>A         p.P1273Q         18         ATP hinge         0.16         0         2           c.3836A>G         p.D1279G         18         ATP hinge         0.24         0         3           c.3848C>T         p.A1283V         18         ATP hinge         0.08         0         1           c.3859G>A         p.G1287S         18         ATP hinge         0.08         0         1           c.3877G>A         p.G1297K         18         ATP hinge         0.08         0         1           c.3884C>T         p.A1293K         18         ATP hinge         0.08         0         1           c.3897G>A         p.E1293K         18         ATP hinge/TM7         0.40         0         5           c.38961>G         p.L1299R         18         ATP hinge/TM7         0.08         0         1           c.3901_3902insA         p.R1301KfsX3         18         ATP hinge/TM7         0.08         0         1           c.3903+5g>a         na         18         ATP hinge/TM7         0.08         0         1           c.3995C>T         p.R1301KfsX3         19         ATP hinge/TM7         0.24         0         3           c.3982G>A         <	c.3818C>T	p.P1273L	18	ATP hinge	0.08	0	1
c.3836A>G       p.D1279G       18       ATP hinge       0.24       0       3         c.3848C>T       p.A1283V       18       ATP hinge       0.08       0       1         c.3859G>A       p.G1287S       18       ATP hinge       0.08       0       1         c.3877G>A       p.G1287S       18       ATP hinge       0.08       0       1         c.3877G>A       p.E1293K       18       ATP hinge       0.08       0       1         c.3884C>T       p.A1295V       18       ATP hinge/TM7       0.40       0       5         c.3896T>G       p.L1299R       18       ATP hinge/TM7       0.08       0       1         c.3901_3902insA       p.R1301KfsX3       18       ATP hinge/TM7       0.08       0       1         c.3903+5g>a       na       18       ATP hinge/TM7       0.08       0       1         c.3903+5g>a       na       18       ATP hinge/TM7       0.08       0       1         c.3985C>T       p.R1301KfsX3       19       ATP hinge/TM7       0.24       0       3         c.3982G>A       p.A1328T       19       TM7       0.24       0       3         c.4005	c.3818C>A	p.P1273Q	18	ATP hinge	0.16	0	2
c.3848C>T       p.A1283V       18       ATP hinge       0.08       0       1         c.3859G>A       p.G1287S       18       ATP hinge       0.08       0       1         c.3877G>A       p.E1293K       18       ATP hinge       0.08       0       1         c.3884C>T       p.E1293K       18       ATP hinge       0.08       0       1         c.3884C>T       p.A1295V       18       ATP hinge/TM7       0.40       0       5         c.3896T>G       p.L1299R       18       ATP hinge/TM7       0.08       0       1         c.3901_3902insA       p.R1301KfsX3       18       ATP hinge/TM7       0.08       0       1         c.3903+5g>a       na       18       ATP hinge/TM7       0.08       0       1         c.3903+5g>a       p.R1301KfsX3       18       ATP hinge/TM7       0.08       0       1         c.3982G>A       p.A1328T       19       ATP hinge/TM7       0.24       0       3         c.4005       p.G1335R       19       TM7       0.16       0       3         c.4005       p.G1335R       19       TM7       0.16       0       3	c.3836A>G	p.D1279G	18	ATP hinge	0.24	0	3
c.3859G>A       p.G1287S       18       ATP hinge       0.06       0       1         c.3857G>A       p.G1287S       18       ATP hinge       0.08       0       1         c.3877G>A       p.E1293K       18       ATP hinge       0.08       0       1         c.3884C>T       p.A1295V       18       ATP hinge/TM7       0.40       0       5         c.3896T>G       p.L1299R       18       ATP hinge/TM7       0.08       0       1         c.3901_3902insA       p.R1301KfsX3       18       ATP hinge/TM7       0.08       0       1         c.3903+5g>a       na       18       ATP hinge/TM7       0.08       0       1         c.3903+5g>a       na       18       ATP hinge/TM7       0.08       0       1         c.3903+5g>a       na       18       ATP hinge/TM7       0.08       0       1         c.3982G>A       p.R1319X       19       ATP hinge/TM7       0.24       0       3         c.4003G>C       p.G1335R       19       TM7       0.24       0       3         c.4005 AutominsTTATAATGGGTTGCG       p.G1335insLXWVA       19       TM7       0.16       0       2   <	c.3848C>T	p.A1283V	18	ATP hinge	0.08	0	1
c.3877G>A       p.E1293K       18       ATP hinge       0.00       0       1         c.3874C>T       p.A1295V       18       ATP hinge/TM7       0.40       0       5         c.3896T>G       p.L1299R       18       ATP hinge/TM7       0.08       0       1         c.3901_3902insA       p.R1301KfsX3       18       ATP hinge/TM7       0.08       0       1         c.3903+5g>a       na       18       ATP hinge/TM7       0.08       0       1         c.39032G>A       p.R1319X       19       ATP hinge/TM7       0.24       0       3         c.4003G>C       p.G1335R       19       TM7       0.16       0       2         c.4005 4006insTTATAATGGGTTGCG       p.G1335insLXWYA       19       TM7       0.16       0       2	c.3859G>A	p.G12875	18	ATP hinge	0.08	0	1
Costror A         p.1125/K         16         ATT hinge         0.06         0         1           c.3884C>T         p.A125/K         18         ATP hinge/TM7         0.40         0         5           c.3884C>T         p.L125/K         18         ATP hinge/TM7         0.08         0         1           c.3896T>G         p.L1299K         18         ATP hinge/TM7         0.08         0         1           c.3901_3902insA         p.R1301KfsX3         18         ATP hinge/TM7         0.08         0         1           c.3903+5g>a         na         18         ATP hinge/TM7         0.08         0         1           c.3955C>T         p.R1319X         19         ATP hinge/TM7         0.24         0         3           c.3982G>A         p.A1328T         19         TM7         0.16         0         2           c.4003G>C         p.G1335R         19         TM7         0.16         0         3	c 3877C>A	p F1293K	18	ATP hingo	0.08	0	- 1
c.3884         p.A1295V         18         A1Phinge/IM7         0.40         0         5           c.3896T>G         p.L1299R         18         ATP hinge/TM7         0.08         0         1           c.3901_3002insA         p.R1301KfsX3         18         ATP hinge/TM7         0.08         0         1           c.3903+5g>a         na         18         ATP hinge/TM7         0.08         0         1           c.3903+5g>a         na         18         ATP hinge/TM7         0.08         0         1           c.3903+5g>a         na         18         ATP hinge/TM7         0.08         0         3           c.3955C>T         p.R1319X         19         ATP hinge/TM7         0.24         0         3           c.3982G>A         p.A1328T         19         TM7         0.16         0         2           c.4005 A006insTTATAATGGGTTIGCG         p.G1335insLXWVA         19         TM7         0.16         0         2	1.30//G/A	P.E1275N	10	ATDI 1	0.00	0	1
c.38961>G         p.L1299R         18         ATP hinge/TM7         0.08         0         1           c.3901_3002insA         p.R1301KfsX3         18         ATP hinge/TM7         0.08         0         1           c.3903+5g>a         na         18         ATP hinge/TM7         0.08         0         1           c.39055>T         p.R1301KfsX3         18         ATP hinge/TM7         0.08         0         1           c.39052>C         p.R1319X         19         ATP hinge/TM7         0.24         0         3           c.3982G>A         p.A1328T         19         TM7         0.16         0         2           c.4005         p.G1335R         19         TM7         0.16         0         2	C.3884C>1	p.A1295V	18	ATPhinge/TM/	0.40	0	5
c.3901_3902insA       p.R1301KfsX3       18       ATP hinge/TM7       0.08       0       1         c.3903+5g>a       na       18       ATP hinge/TM7       0.08       0       1         c.3955C>T       p.R1319X       19       ATP hinge/TM7       0.24       0       3         c.3982G>A       p.A1328T       19       TM7       0.16       0       2         c.4003G>C       p.G1335R       19       TM7       0.16       0       3         c.4005 4006insTTATAATGGGTTGCG       p.G1335insLXWVA       19       TM7       0.16       0       2	c.3896T>G	p.L1299R	18	ATP hinge/TM7	0.08	0	1
c.3903+5g>a       na       18       ATP hinge/TM7       0.08       0       1         c.3955C>T       p.R1319X       19       ATP hinge/TM7       0.24       0       3         c.3982G>A       p.A1328T       19       TM7       0.16       0       2         c.4003G>C       p.G1335R       19       TM7       0.24       0       3         c.4005 4006insTTATAATGGGTTGCG       p.G1335insLXWA       19       TM7       0.16       0       2	c.3901_3902insA	p.R1301KfsX3	18	ATP hinge/TM7	0.08	0	1
c.3955C>T     p.R1319X     19     ATP hinge/TM7     0.24     0     3       c.3982G>A     p.A1328T     19     TM7     0.16     0     2       c.4003G>C     p.G1335R     19     TM7     0.24     0     3       c.4005 4006insTTATAATGGGTTGCG     p.G1335insLXWVA     19     TM7     0.16     0     2	c.3903+5g>a	na	18	ATP hinge/TM7	0.08	0	1
c.3982G>A p.A1328T 19 TM7 0.16 0 2 c.4003G>C p.G1335R 19 TM7 0.24 0 3 c.4005 4006insTTATAATGGGTTGCG p.G1335insLXWVA 19 TM7 0.16 0 2	c.3955C>T	p.R1319X	19	ATP hinge/TM7	0.24	0	3
c.4003G>C p.G1335IR 19 TM7 0.24 0 3 c.4005 4006insTTATAATGGGTTGCG p.G1335insLXWVA 19 TM7 0.16 0 2	c.3982G>A	p.A1328T	19	TM7	0.16	0	2
c.4005 4006insTTATAATGGGTTGCG p.G1335insLXWVA 19 TM7 0.16 0 2	c.4003G>C	p.G1335R	19	TM7	0.24	0	3
	c.4005 4006insTTATAATGGGTTGCG	p.G1335insLXWVA	19	TM7	0.16	0	2

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Mutation analysis			Domain	Frequency of M	MU (%) No. of patien	No. of patients	
Nucleotide mutation	Protein alteration	Exon			MU/MU	WT/MU	
c.4057T>C	p.W1353R	20	TM8	0.16	0	2	
c.4059G>A	p.W1353X	20	TM8	0.08	0	1	
c.4064G>A	p.G1355D	20	TM8	0.08	0	1	
c.4112T>C	p.L1371P	20	TM8	0.40	0	5	
c.4114C>T	p.Q1372X	20	TM8	0.63	0	8	
c.4162delG	p.A1388RfsX5	21	after TM8	0.08	0	1	
c.4272T>G	p.Y1424X	21	after TM8	0.08	0	1	

MU: mutant; WT: wild type; Cu: copper binding domain; Td: transduction domain converting energy from ATP hydrolysis to cation transportation; Tm: transmembrane domain; Ch: ion channel; Ph: phosphorylation loop.

Table 3. Classified n	nutations within	100 missense	mutations.
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Nucleotide	Protein	Exon	Sift		PolyPhen 2		1000g	ExAc	Classification	Evidence of
mutation	alteration		Score	Prediction	Score	Prediction	_			pathogenicity
c.588C>A	p.D196E	2	1	Tolerated	0.924	Probably damaging	0	5	US	4*PP
c.592A>G	p.R198G	2	0.05	Damaging	0.994	Probably damaging	0	0	LP	1*PM,4*PP
c.1168A>G	p.I390V	2	0.57	Tolerated	0.001	Benign	0	2	LB	1*BS,1*BP
c.1426G>A	p.A476T	3	0.63	Tolerated	0.503	Possibly damaging	2	53	US	1*BS
c.1544G>T	p.G515V	4	0	Damaging	1	Probably damaging	0	0	Р	1*PS,2*PM,5*PP
c.1760C>T	p.T587M	5	0.19	Tolerated	0.099	Benign	0	0	LB	1*BS,1*BP
c.1817T>G	p.V606G	5	0	Damaging	1	Probably damaging	0	0	LP	1*PM,5*PP
c.1846C>T	p.R616Y	5	0	Damaging	1	Probably damaging	0	4	LP	2*PM,5*PP
c.1925A>G	p.D642G	6	0.01	Damaging	1	Probably damaging	0	0	LP	1*PM,4*PP
c.2078C>G	p.S693C	7	0.01	Damaging	1	Probably damaging	0	0	Р	1*PS,2*PM,5*PP
c.2128G>A	p.G710S	8	0.02	Damaging	1	Probably damaging	0	0	Р	1*PS,2*PM,5*PP
c.2156A>G	p.Y719C	8	0	Damaging	0.991	Probably damaging	0	0	LP	2*PM,4*PP
c.2192T>A	p.V731E	8	0	Damaging	1	Probably damaging	0	0	Р	1*PS,2*PM,5*PP
c.2195T>C	p.L732P	8	0	Damaging	1	Probably damaging	0	0	Р	1*PS,2*PM,5*PP
c.2251G>T	p.A751S	8	0.16	Tolerated	0.999	Probably damaging	0	0	LP	2*PM,3*PP
c.2261A>G	p.E754G	8	0.34	Tolerated	0.999	Probably damaging	0	0	LP	2*PM,3*PP
c.2267C>G	p.A756G	8	0.21	Tolerated	1	Probably damaging	0	0	Р	1*PS,2*PM,5*PP
c.2294A>G	p.D765G	8	0	Damaging	1	Probably damaging	0	0	LP	3*PM,5*PP
c.2297C>T	p.T766M	8	0	Damaging	1	Probably damaging	0	1	Р	1*PS,2*PM,5*PP
c.2305A>G	p.M769V	8	0	Damaging	1	Probably damaging	0	8	LP	3*PM,5*PP
c.2308C>T	p.L770F	8	0	Damaging	1	Probably damaging	0	0	LP	2*PM,4*PP
c.2332C>T	p.R778W	8	0	Damaging	1	Probably damaging	0	5	Р	2*PS,3*PM
c.2333G>A	p.R778Q	8	0	Damaging	1	Probably damaging	0	5	Р	2*PS,3*PM
c.2333G>T	p.R778L	8	0	Damaging	1	Probably damaging	0	5	Р	2*PS,3*PM
c.2341G>A	p.E781K	8	0	Damaging	1	Probably damaging	0	0	Р	1*PS,2*PM,4*PP
c.2383C>T	p.L795F	9	0	Damaging	1	Probably damaging	0	4	Р	1*PS,3*PM
c.2390C>T	p.S797F	9	0	Damaging	1	Probably damaging	0	0	LP	1*PM,4*PP
c.2525A>G	p.D842G	10	0	Damaging	1	Probably damaging	0	0	LP	1*PM,4*PP
c.2587C>T	p.P863S	11	0	Damaging	1	Probably damaging	0	0	LP	1*PM,4*PP
c.2605G>A	p.G869R	11	0	Damaging	1	Probably damaging	5	82	LP	2*PM,5*PP
c.2620G>C	p.A874P	11	0.01	Damaging	1	Probably damaging	0	0	LP	2*PM,5*PP
c.2621C>T	p.A874V	11	0.01	Damaging	1	Probably damaging	0	9	LP	2*PM,5*PP
c.2662A>C	p.T888P	11	0	Damaging	1	Probably damaging	0	0	LP	2*PM,5*PP
c.2668G>A	p.V890M	11	0.01	Damaging	1	Probably damaging	0	0	LP	2*PM,5*PP
c.2755C>G	p.R919G	12	0.01	Damaging	0.988	Probably damaging	0	2	Р	1*PS,2*PM,5*PP
c.2804C>T	p.T935M	12	0	Damaging	1	Probably damaging	0	21	Р	1*PS,1*PM,5*PP
c.2827G>A	p.G943S	12	0.16	Tolerated	1	Probably damaging	0	2	Р	1*PS,1*PM,4*PP
c.2828G>A	p.G943D	12	0	Damaging	1	Probably damaging	0	2	Р	1*PS,2*PM,5*PP
c.2848G>T	p.V950F	12	0.01	Damaging	0.994	Probably damaging	0	0	LP	2*PM,4*PP
c.2905C>T	p.R969W	13	0.02	Damaging	1	Probably damaging	0	5	LP	2*PM,5*PP
c.2924C>A	p.S975Y	13	0.01	Damaging	1	Probably damaging	0	1	LP	2*PM,5*PP
c.2930C>T	p.T977M	13	0	Damaging	1	Probably damaging	0	10	Р	1*PS,2*PM,5*PP
c.2957C>T	p.S986F	13	0	Damaging	1	Probably damaging	0	0	LP	2*PM,5*PP
c.2975C>T	p.P992L	13	0	Damaging	1	Probably damaging	0	5	Р	2*PS,3*PM
c.3007G>A	p.A1003T	13	0	Damaging	1	Probably damaging	1	2	LP	2*PM,5*PP
c.3008C>T	p.A1003V	13	0	Damaging	1	Probably damaging	0	7	LP	2*PM,5*PP
c.3029A>C	p.K1010T	13	0	Damaging	1	Probably damaging	0	0	Р	1*PS,2*PM,5*PP
c.3044T>C	p.L1015P	13	0	Damaging	1	Probably damaging	0	0	LP	2*PM,4*PP
c.3053C>T	p.A1018V	13	0.07	Tolerated	1	Probably damaging	0	3	LP	2*PM,5*PP
c.3083A>G	p.K1028R	14	0.02	Damaging	0.998	Probably damaging	0	0	LP	2*PM,4*PP
c.3089G>A	p.G1030D	14	0	Damaging	1	Probably damaging	0	0	LP	2*PM,5*PP
c.3095T>C	p.I1032T	14	0	Damaging	0.998	Probably damaging	0	0	LP	2*PM,4*PP
c.3098C>T	p.T1033I	14	0.01	Damaging	1	Probably damaging	0	0	Р	1*PS,2*PM,4*PP

Nucleotide	Protein	Exon	Sift		PolyPhen 2		1000g	ExAc	Classification	Evidence of
mutation	alteration		Score	Prediction	Score	Prediction	_ 0			pathogenicity
c.3104G>T	p.G1035V	14	0	Damaging	1	Probably damaging	0	0	LP	2*PM,5*PP
c.3121C>T	p.R1041W	14	0	Damaging	1	Probably damaging	0	5	LP	2*PM,5*PP
c.3122G>C	p.R1041P	14	0.01	Damaging	1	Probably damaging	0	0	LP	2*PM,5*PP
c.3140A>T	p.D1047V	14	0.13	Tolerated	0.997	Probably damaging	0	0	LP	2*PM,4*PP
c.3155C>T	p.P1052L	14	0.06	Tolerated	0.998	Probably damaging	0	1	LP	2*PM,4*PP
c.3209C>G	p.P1070R	14	0	Damaging	1	Probably damaging	0	0	LP	2*PM,4*PP
c.3221C>T	p.A1074V	14	0	Damaging	1	Probably damaging	0	0	LP	2*PM,5*PP
c.3263T>C	p.L1088S	15	0.2	Tolerated	1	Probably damaging	0	0	LP	1*PS,1*PM,3*PP
c.3271T>C	p.C1091R	15	0	Damaging	0.96	Probably damaging	0	0	LP	1*PM,4*PP
c.3274A>C	p.T1092P	15	0.11	Tolerated	0.832	Possibly damaging	0	0	US	1*PM,3*PP
c.3311G>A	p.C1104Y	15	0	Damaging	1	Probably damaging	0	1	Р	1*PS,2*PM,5*PP
c.3316G>A	p.V1106I	15	0.15	Tolerated	0.984	Probably damaging	2	16	Р	1*PS,2*PM,4*PP
c.3368C>T	p.P1123L	15	0.31	Tolerated	0.025	Benign	0	25	LB	1*BS,1*BP
c.3426G>C	p.Q1142H	16	0.16	Tolerated	0.007	Benign	0	3	LB	1*BS,1*BP
c.3443T>C	p.I1148T	16	0	Damaging	0.999	Probably damaging	0	5	LP	1*PM,5*PP
c.3446G>A	p.G1149E	16	0	Damaging	1	Probably damaging	0	0	Р	1*PS,2*PM,5*PP
c.3451C>G	p.R1151G	16	0	Damaging	1	Probably damaging	0	0	Р	1*PS,1*PM,4*PP
c.3451C>T	p.R1151C	16	0	Damaging	1	Probably damaging	0	5	Р	1*PS,1*PM,4*PP
c.3452G>A	p.R1151H	16	0.01	Damaging	1	Probably damaging	0	2	LP	3*PM,5*PP
c.3459G>T	p.W1153C	16	0	Damaging	1	Probably damaging	0	0	LP	3*PM,5*PP
c.3517G>A	p.E1173K	16	0	Damaging	1	Probably damaging	0	1	LP	3*PM,5*PP
c.3532A>G	p.T1178A	16	0	Damaging	0.988	Probably damaging	0	0	LP	1*PM,5*PP
c.3563T>G	p.L1188R	17	0	Damaging	0.998	Probably damaging	0	0	LP	1*PM,4*PP
c.3587A>G	p.D1196G	17	0	Damaging	1	Probably damaging	0	0	LP	1*PM,4*PP
c.3605C>G	p.A1202G	17	0	Damaging	1	Probably damaging	0	0	LP	1*PM,4*PP
c.3646G>A	p.V1216M	17	0	Damaging	1	Probably damaging	0	5	LP	1*PM,4*PP
c.3653T>C	p.L1218P	17	0	Damaging	0.999	Probably damaging	0	0	LP	1*PM,4*PP
c.3715G>T	p.V1239F	18	0	Damaging	0.998	Probably damaging	0	2	Р	1*PS,1*PM,4*PP
c.3733C>G	p.P1245A	18	0	Damaging	1	Probably damaging	0	0	LP	1*PM,4*PP
c.3741C>G	p.H1247Q	18	0.17	Tolerated	1	Probably damaging	0	1	LP	1*PM,4*PP
c.3776G>T	p.G1259V	18	0	Damaging	0.997	Probably damaging	0	0	LP	1*PM,4*PP
c.3791T>C	p.M1264T	18	0	Damaging	0.998	Probably damaging	0	0	LP	1*PM,4*PP
c.3802G>A	p.G1268R	18	0	Damaging	1	Probably damaging	0	0	LP	2*PM,5*PP
c.3809A>G	p.N1270S	18	0	Damaging	1	Probably damaging	0	18	Р	1*PS,2*PM,5*PP
c.3818C>A	p.P1273Q	18	0	Damaging	1	Probably damaging	0	0	Р	1*PS,2*PM,5*PP
c.3818C>T	p.P1273L	18	0	Damaging	1	Probably damaging	0	4	Р	1*PS,2*PM,5*PP
c.3836A>G	p.D1279G	18	0.01	Damaging	1	Probably damaging	0	2	LP	2*PM,5*PP
c.3848C>T	p.A1283V	18	0	Damaging	1	Probably damaging	0	0	LP	2*PM,5*PP
c.3859G>A	p.G1287S	18	0	Damaging	1	Probably damaging	0	3	Р	1*PS,2*PM,5*PP
c.3877G>A	p.E1293K	18	0	Damaging	1	Probably damaging	0	1	LP	2*PM,5*PP
c.3884C>T	p.A1295V	18	0	Damaging	1	Probably damaging	0	0	Р	1*PS,2*PM,4*PP
c.3896T>G	p.L1299R	18	0	Damaging	0.999	Probably damaging	0	0	Р	1*PS,2*PM,4*PP
c.3982G>A	p.A1328T	19	0	Damaging	1	Probably damaging	0	0	LP	1*PM,5*PP
c.4003G>C	p.G1335R	19	0	Damaging	1	Probably damaging	0	0	LP	1*PM,5*PP
c.4057T>C	p.W1353R	20	0	Damaging	1	Probably damaging	0	0	LP	2*PM,5*PP
c.4064G>A	p.G1355D	20	0	Damaging	1	Probably damaging	0	0	LP	2*PM,5*PP
c.4112T>C	p.L1371P	20	0.01	Damaging	1	Probably damaging	0	0	LP	1*PM,5*PP

PolyPhen 2/ SIFT: Software prediction programs used for sequence variant effect explanation; 1000g: 1000 Genomes Project; ExAc: Exome Aggregation Consortium.

## **Novel Variants**

Among the 161 non-synonymous variants, 58 are novel and the chromatograms of these variants were illustrated in **Figures 2A**, **2B**, **2C** and **2D**, grouped by the type of variation. None of which was found in the 503 normal individuals. Of these 58 novel variants, 16 are small deletions or insertions, 4 are nonsense variants, 6 are splice site variants, and 32 are missense variants. The other 103 variants have been recorded in the professional version of HGMD (Human Gene Mutation Database Professional, access date: 20 October, 2015).

Among the 16 small deletions or insertions, 13 alter the reading frame of *ATP7B* and result in pro-

duction of a truncated dysfunctional protein. They are c.268\_271del (p.K90FfsX10), c.367delG (p.A123Pfs X30), (p.P232QfsX30), c.1403\_1416del c.695delC (p.A468GfsX33), c.1545delT (p.G515GfsX9), c.1552 1553delTC (p.S518RfsX15), c.2043delC (p.S681SfsX15), c.2794\_2795insGT (p.S932CfsX4), c.2853\_2856delGAGA (p.Q951HfsX15), c.3377\_3378de 1AC (p.H1126PfsX3), c.3766\_3767dupCA (p.Q1256Pfs X75), c.3901\_3902insA (p.R1301KfsX3) and c.4162delG (p.A1388RfsX5). The other 3 small deletions or insertions, c.2316\_2317insCTCTTTGTG (p.V772insLFV),c.2 790\_2792delCAT (p.I930del) and c.4005\_4006insTTAT AATGGGTTGCG (p.G1335insLXWVA) do not change the reading frame of ATP7B, but cause prolonged (p.V772insLFV and p.G1335insLXWVA) or shortened (p.I930del) dysfunctional ATP7B protein.

Similarly, the 4 nonsense variants could result in production of a shortened, dysfunctional protein.

Α		\ 476T	T597M	D642C	X7400	47540	57540	1 7705
-						A7515	E754G	
					<u>NM WAYN</u>		₩ <u>₩</u> ₩	
	T1033I	P1070R	L1088S	C1091R	T1092P	P1123L	R1151G	L1188R-
		And the second	<u>хий</u>	<u> Yww.</u>			MMM.	
	D1196G					Μ1264Τ		
			$\bigvee \bigvee $			<u>้</u>		
В	K0056-X40	410006-100	D2220fe¥20	A46906-¥22	05450620	054006-245	000406-145	VZZQinal EV/
		-A123F18A30-	- F 232QISA30-	-A400GISA33-	001001879	- 35 TORISA 15 -	_ 3001315/13 _	
		M. M	WWWW					
	MMMM			MANAAcomp				MAAM
	1930del	S932CfsX4	Q951HfsX15	H1126PfsX3	Q1256PfsX75	R1301KfsX3	G1335insLXWVA	A1388RfsX5
			alle himle Manage		Malan			M.M.M.M.M.
		Manan	Mielandulananaan				MM Moral An Americanan	<u></u>
С	51+1g≥a	—1543+4a≥q —	—1946+5α≥a−	—2356-1q>c—	—3557-2a≥q—			
		MANA				<u>vôvůvů</u> ť		
D	)		W1353Y	V1424V				
	MMM	AMAMA	MMM	MMM				

Figure 2: Chromatograms of 58 novel ATP7B variants identified in the present study. The lower chromatogram in each frame represents the variant, while the upper one represents the normal sequence. The c.4162delG variant is shown in reverse sequence, while the other 57 variants are illustrated in forward sequence. 2A, 2B, 2C and 2D respectively illustrates 32 missense changes, 16 small deletions or insertions, 6 splicing site variants as well as 4 nonsense variants.

	R198G	A476T	T587M	D642G	Y719C	A751S	E754G
ATP7B-Human LOC452734-Troglodytes ATP7B-Mouse ATP7B-Rat ATP7B-Cattel ATP7B-Dog ATP7B-Monkey ATP7B-Chicken	EDLRDHV EDLRDHV EDLRDHI EDLRDHI QDLRDHI QDLRDHV EDLRDHV EDLRDHV EELRSHI	DILAKSP DILAKSP GHSSETP GYLSDSP RQSPKSL GRPSRSP DIWAKSP SPHLDEP	SKLTRTN SKLTRTN SKLTRTN SKLTRTN SKLRRTE SKLTRMA SKLTRTN SKLMRTN	HHLDHKM RHLDHKM HHLDHKT HHLDHKT HHLDHKV HHLDHKV HHLDHKM HNLDHKK	VQAYKSL VQAYKSL VQAYKSL VQAYKSL VQAYKSL VQAYKSL VQAYKSL IQAYKSL	LVVAVAE LVVAVAE LVVA IAE LVVA IAE LVVAVAE LVVAVAE LVVAVAE LVVAVAE LLVAI IE	AVAE KAE AVAE KAE AVAE KAE A IAE KAE AVAE KAE AVAE KAE AVAE KAE AII E KAE
	L770F	E781K	S797F	D842G	P863S	V950F	L1015P
ATP7B-Human LOC452734-Troglodytes ATP7B-Mouse ATP7B-Rat ATP7B-Cattel ATP7B-Dog ATP7B-Monkey ATP7B-Chicken	PPMLFVF PPMLFVF PPMLFVF PPMLFVF PPMLFVF PPMLFVF PPMLFVF PPMLFVF	RWLEHLA RWLEHVA RWLEHVA RWLEHVA RWLEHVV RWLEH IA RWLEHLA RWLEH IA	KLMSLQA KLMSLQA KLMSLQA KLMSLQA KLMSLQA KLMSLQA KLMSLQA KLI SLQA	FPVDGKV FPVDGKV FPVDGKV FPVDGKV FPVDGKV FPVDGKV FPVDGKV FPVDGKV	EAMPVTK EAMPVTK EAMPVTK EAMPVTK EAMPVTK EAACFIG EAMPVTK	FGVVQRY FGVVQKY FGVVQKY FGVVQKY FGVVQKY FGVVQKY FDIIQKY	GKPLEMA GKPLEMA GKPLEMA GKPLEMA GKPLEMA GKPLEMA GKPLEMA
	K1028R	I1032T	T1033I	P1070R	L1088S	C1091R	T1092P
ATP7B-Human LOC452734-Troglodytes ATP7B-Mouse ATP7B-Rat ATP7B-Cattel ATP7B-Dog ATP7B-Monkey ATP7B-Chicken	MFDKTGT MFDKTGT MFDKTGT MFDKTGT MFDKTGT MFDKTGT MFDKTGT	TGTITHG TGTITHG TGTITHG TGTITHG TGTITHG TGTITHG TGTITHG TGTITCG	GTITHGV GTITHGV GTITHGV GTITHGV GTITHGV GTITHGV GTITHGV GTITCGV	SEHPLGV SEHPLGV SEHPLGV SEHPLGV SEHPLGV SEHPLGV SEHPLGV SEHPLGV	TETLGYC TETLGYC TETLGYS TETLGYS TETLGCC TETLGYC TETLGYC TQSLGYC	LGYCTNF LGYCTDF LGYSTDF LGYSTDF LGCCTDF LGYCTDF LGYCTDF LGYCTDF	GYCTDFQ GYCTDFQ GYSTDFQ GYSTDFQ GCCTDFQ GYCTDFQ GYCTDFQ GYCTDFQ
	P1123L	R1151G	L1188R	D1196G	L1218P	V1239F	P1245A
ATP7B-Human LOC452734-Troglodytes ATP7B-Mouse ATP7B-Rat ATP7B-Cattel ATP7B-Dog ATP7B-Dog ATP7B-Monkey ATP7B-Chicken	LSAPASH LRALASH RSDLASH HRGPTSH QGPLTTH RSKQAAP LSAPASH VDKLDVN	IGNREWL IGNREWL IGNREWM IGNREWM IGNREWM IGNREWL IGNREWM	DGVLCGM DGVLCGM DGVLCGM DGVLCGM DGVLCGM DGVLCGM DGVLCGM DGALCGM	AIADAVK AIADAVK AIADAVK AIADAVK AIADAVK AIADAVK AIADAVK AIADAVK	DVVLITG DVVLITG DVALITG DVALITG DVVLITG DVVLITG DVVLITG DVVLITG	INKVFAE INKVFAE INKVFAE INKVFAE INKVFAE INKVFAE INKVFAE IKKVFAE	EVLPSHK EVLPSHK EVLPSHK EVLPSHK EVLPSHK EVLPSHK EVLPSHK EVLPSHK
	G1259V	M1264T	A1283V	L1299R			
ATP7B-Human LOC452734-Troglodytes ATP7B-Mouse ATP7B-Rat ATP7B-Cattel ATP7B-Dog ATP7B-Monkey ATP7B-Chicken	QNKGKKV QNKGKKV QNEGKKV QNKGKKV QNEGKRV QNEGKKV QNEGKRV QNGRRKV	KVAMVGD KVAMVGD KVAMVGD RVAMVGD KVAMVGD RVAMVGD KVAMVGD	MGVAIGT MGVAIGT VGIAIGT VGIAIGT VGIAIGT VGIAIGT MGVAIGT IGIAIGT	DVVLIRN DVVLIRN DVVLIRN DVVLIRN DVVLIRN DVVLIRN DVVLIRN DVVLIRN			
Figure 3: Homology comparisons of ATP7B pro	tein sequences.	The highlighted a	zones respective	ly indicate 32 n	ovel missense v	ariant sites am	ong 8 species.

For six splice site variants, three (c.51+1g>a, c.2356-1g>c and c.3557-2a>g) are classified as 'pathogenic variants', the other three (c.1543+4a>g)c.1946+5g>a, 3903+5g>a) are 'variants with uncertain significance'. In addition, among the 32 novel missense variants, 2 (p.T587M, p.P1123L) are classified as 'likely benign variants', 2 (p.A476T, p.T1092P) as 'variants with uncertain significance', 5 (p.E781K, p.T1033I, p.R1151G, p.V1239F, p.L1299R) as 'pathogenic variants' and the other 23 as 'likely pathogenic variants' (Table 3). A homology search of the ATP7B protein in different species demonstrated that 32 missense variants occur within highly conserved regions of ATP7B protein (Figure 3). In total, among 58 novel variants, 25 are classified as 'pathogenic variants', 26 as 'likely pathogenic variants', 5 as 'variants with uncertain significance' and 2 as 'likely benign variants'.

#### **Most Common Variants**

Among the 632 WD patients, 569 patients (90%) were identified with homozygous or compound heterozygous potential disease-causing variants, 58 patients (9%) with one heterozygous variant and other 5 patients (1%) did not have any potential disease-causing variant. Therefore, 90% (569/632) of patients can be genetically diagnosed with WD. Among the 142 potential disease-causing variants including 78 'pathogenic variants' and 64 'likely pathogenic variants', 14 were relatively common in the WD patient cohort, each with an allelic frequency 1% or higher. These 14 most common disease-causing variants were found in 94% (537/569) of genetically diagnosed WD patients with two or more 'pathogenic' or 'likely pathogenic' variants. The allelic frequencies and numbers of patients with each of these variant are presented in Table 4. Notably, the three most prevalent variants, p.R778L, p.P992L and p.T935M, were

detected at least once in 78% (445/569) of genetically diagnosed WD patients. The allelic frequencies of p.R778L, p.P992L and p.T935M are 0.319, 0.155 and 0.077, respectively; all of which are 'pathogenic variants'.

#### Patients with More than Two Variants

Six patients carried three disease-causing variants and their 3-variant genotypes are described in

Tab	le 4.	Common	disease-causing	variants	within ATP7E	3 among <b>569</b>	WD patients
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**Figure 4**. As two patients had the same genotype, there are 5 unique 3-variant genotypes. Four of these 3-variant genotype include at least one 'likely pathogenic' variant, while one genotype (T935M+G943D+V1106I) consists of three 'pathogenic' variants.

Mutation	Domain affected	Number of pat	ients		Allelic	Classification
		WW	WM	MM	Frequencies	
p.R778L	TM4	270	235	64	0.319	Pathogenic
p.P992L	TM6/Ph	419	124	26	0.155	Pathogenic
p.T935M	TM5	482	86	1	0.077	Pathogenic
p.A874V	Td/TM5	529	37	3	0.038	Likely pathogenic
p.I1148T	ATP loop	530	38	1	0.035	Likely pathogenic
p.Q511X	Cu5	541	26	2	0.026	Pathogenic
p.G943D	TM5	543	25	1	0.024	Pathogenic
p.N1270S	ATP hinge	544	25	0	0.022	Pathogenic
p.R778Q	TM4	548	18	3	0.021	Pathogenic
p.R919G	Td/TM5	545	24	0	0.021	Pathogenic
p.V1216M	ATP bind	547	20	2	0.021	Likely pathogenic
p.V176SfsX28	Cu2	551	17	1	0.017	Pathogenic
c.1708-1g>c	Cu6	553	14	2	0.016	Pathogenic
p.V1106I	ATP loop	556	13	0	0.011	Pathogenic

WW: neither of chromosome carries mutation; WM: one chromosome carries mutation;

MM: both chromosomes carry mutations.



### Discussion

In the present study, the prevalence of *ATP7B* variants was systematically investigated in the largest Chinese WD cohort to date, with 632 patients and 503 normal controls. One hundred and sixty-one non-synonymous variants within the *ATP7B* gene were found in WD patients, including 58 novel variants. This study catalogs *ATP7B* variants in Han Chinese WD patients and expands the spectrum of *ATP7B* variants.

Another major contribution of the study is the classification of *ATP7B* variants. Based on the type of alterations, their predicted impact, and frequency between WD cases and controls, these 161 non-synonymous variants are classified as 'patho-

genic variants' (N=78), 'likely pathogenic variants' (N=64), 'variants with uncertain significance' (N=8), 'likely benign variants' (N=4), and 'benign variants' (N=7). The observation that 90% (569/632) of these WD patients had two or more 'pathogenic' or 'likely pathogenic' variants demonstrates the clinical utility of the catalog and classification of *ATP7B* variants.

The 14 most common disease-causing variants were found at least once in 94% (537/569) of genetically diagnosed patients. Notably, the three most prevalent pathogenic variants, p.R778L, p.P992L and p.T935M, were detected in 78% (445/569) of the patients. These results demonstrate the feasibility of developing a rapid and cost-effective genetic test such as multiplex allele-specific PCR to screen for WD.

We found 6 unrelated WD patients (1.1%) carrying three disease-causing variants, and which was reported previously in Caucasian populations.<sup>6</sup> This observation is important because it suggests that two disease-causing variants may reside in a chromosome. The implication is that if an individual carries two disease-causing variants but his/her clinical features do not support the diagnosis of WD, it is necessary to test these variants in parents to identify the specific location of them. If the two variants reside in a chromosome, the individual is a heterozygous carrier and cannot be genetically diagnosed. If two variants reside in different chromosomes, then a genetic diagnosis of

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#### WD can be made.

According to ACMG Standards and Guidelines,12 we classified 4 variants as 'likely benign' variants, one of which (p.Q1142H) was previously considered as a pathogenic variant.<sup>14</sup> Tsai et al. found that Q1142 was located at the ATP pocket of ATP7B protein, and the amino acid replacement of the site would directly disrupt ATP7B function. However, the amino acid change in p.Q1142H was predicted to be tolerated by SIFT (score: 0.16) and benign by PolyPhen-2 (score: 0) software programs, this variant should be considered as 'likely benign'. This finding is important because the variant is relatively frequent and found in 19 WD patients (18 heterozygous and one homozygous). Caution should be made in interpreting the carrier of the Q1142 variant to avoid misdiagnosis and unnecessary treatment.

Sixty-three clinically diagnosed WD patients cannot be genetically diagnosed with WD because they were detected to carry only one disease-causing variant or none. Several factors may induce the observation. First, a subset of these 63 patients may have been misdiagnosed. For example, these patients may have been included in the patient cohort on the basis of false positive K-F rings. Second, large hemizygous deletions may occur in a subset of these patients and these alterations are difficult to be detected using the Sanger sequencing method. In fact, a hemizygous large deletion spanning the exon 20 and adjacent introns has previously been reported.<sup>15</sup> Other methods such as multiplex ligation-dependent probe amplification (MLPA) may be used to detect large deletions. Third, other genetic alterations outside the ATP7B coding region and adjacent splice sites as well as other cellular factors associated with WD may contribute to the clinical development of WD in these patients.<sup>16</sup>

In conclusion, the current study considerably expands the spectrum of *ATP7B* variants and provides classification of their clinical effects. These results improve the genetic diagnosis of suspected WD patients and facilitate genetic screening for WD among asymptomatic children in the general Chinese population.

#### Abbreviations

Cp: ceruloplasmin; K-F: Kayser-Fleischer; ACMG: American College of Medical Genetics and Genomics; HGMD: Human Gene Mutation Database; MLPA: multiplex ligation-dependent probe amplification.

## Supplementary Material

Supplementary Table S1. http://www.thno.org/v06p0638s1.pdf

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## **Conflicts of Interest**

All authors reported no biomedical financial interests or potential conflicts of interest.

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