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SHORT COMMUNICATION

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Novel mutations of the *ATP7B* gene in Japanese patients with Wilson disease

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Abstract Wilson disease (WD) is an autosomal recessive disorder characterized by copper accumulation in the liver, brain, kidneys, and corneas, and culminating in copper toxication in these organs. In this study, we analyzed mutations of the responsible gene, *ATP7B*, in four Japanese patients with WD. By direct sequencing, we identified five mutations, of which two were novel, and 16 polymorphisms, of which 6 were novel. The mutations 2871delC and 2513delA shift the reading frame so that truncated abnormal protein is expected. In contrast to these mutations found in patients with hepatic-type of early onset, the mutations A874V, R778L, and 3892delGTC were either missense mutations or inframe 1-amino acid deletion, and occurred in the patients with hepato-neurologic type of late onset. The mutations 2871delC and R778L have been previously reported in a relatively large number of Japanese patients. In particular, R778L is known to be more prevalent in Asian countries than in other countries of the world. Our data are compatible with the hypothesis that the mutations tend to occur in a population-specific manner. Therefore, the accumulation of the types of mutations in Japanese patients with WD will facilitate the fast and effective genetic diagnosis of WD in Japanese patients.

Key words Wilson disease · *ATP7B* gene · Mutation · Polymorphism · Japanese

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Introduction

Wilson disease (WD; MIM #277900) is an autosomal recessive disorder characterized by copper accumulation in the liver, skin, brain, and kidneys, and culminating in the copper toxication in these organs. WD usually manifests early with chronic liver disease, or later with neuropsychiatric impairment, and sometimes demonstrates additional kidney malfunction and also affects the blood, bones, heart, and connective tissue. Treatment involves the removal of excess copper from the tissue by the use of such chelating agents as D-penicillamine or trientine, or by blocking intestinal copper absorption with zinc salts. It is also necessary for patients to avoid eating foods with a high copper content, such as liver, chocolate, nuts, mushrooms, legumes, and shellfish. The prevalence of the disease is approximately 1 in 30,000, with a carrier frequency of approximately 1 in 90 (Scheinberg and Sternlieb 1984).

The gene for WD, which is located on chromosome 13q14.3, has been cloned and the gene, *ATP7B*, has also been isolated. The *ATP7B* gene consists of 21 exons which span a genomic region of about 80 kb, and encodes a protein of 1,465 amino acids, P-type copper-transporting adenosine triphosphatase (ATPase) (Bull et al. 1993; Tanzi et al. 1993; Petrukhin et al. 1994), which has high amino acid identity with that of the gene for Menkes disease (ATP7A; MIM #300011), an X-linked disorder of copper transport. Characterization of the exon-intron boundaries of the gene for WD has recently made it possible to carry out mutation analyses in patients with WD (Petrukhin et al. 1994). Mutation screening has thus led to the identification of at least 138 disease-specific mutations in the world (Human Gene Mutation Database), among which 20 mutations have been found in Japanese patients. To further clarify the population-specific mutations and the genotype-phenotype correlations in WD, we analyzed the genomic sequence of the *ATP7B* gene in our four patients with WD, who are all residents of Oita prefecture in Japan.

Patients and methods

Subjects

Four Japanese patients with WD from three unrelated families, their parents, and three normal individuals were examined for mutations and polymorphisms in the *ATP7B* gene. The diagnosis of the patients was based on the clinical symptoms, laboratory studies of copper levels in serum and urine, serum ceruloplasmin levels, and biopsy specimens of liver tissue.

Case reports

The clinical and laboratory findings of the patients examined are shown in Table 1. Case 1 was a 16-year-old boy who had suffered from fulminant type liver damage and hemolytic anemia. He was suspected of having WD at the age of 16, and his serum levels of ceruloplasmin and copper, and urinary copper excretion were therefore examined. He was diagnosed with liver-type WD, based on the laboratory data and clinical symptoms. Hepatic failure was treated with plasma exchange, and he is presently medicated with trientine. As he was diagnosed with WD, an examination of his family members was carried out. Case 2, the younger brother of case 1, had no symptoms, and was screened for WD at the age of 14. His serum ceruloplasmin level was extremely low (Table 1) and a biopsy specimen of his liver revealed chronic hepatitis, and a diagnosis of WD was made. He is now being treated with penicillamine. Cases 1 and 2 had Kayser-Fleischer rings. There was no consanguinity in this kindred. Although the father's serum ceruloplasmin level was low, he did not show any liver abnormality, as is compatible with the evidence that 10%–20% of normal carriers show low levels of serum ceruloplasmin (Gibbs and Walshe 1979).

Case 3 was a 38-year-old man. He developed hand tremor at the age of 27, suffered from liver cirrhosis, and experienced rupture of esophageal varices at the age of 28. He had Kayser-Fleischer rings and was diagnosed with hepato-neurologic type of WD. He was treated with penicillamine. There was no consanguinity in his kindred.

Case 4 was a 42-year-old man. His father had liver cirrhosis, and his older brother had died of multiple organ failure caused by WD. There was no consanguinity in his kindred. He had Kayser-Fleischer rings and was diagnosed with WD at the age of 22. He was diagnosed with liver cirrhosis at the age of 40 and received sclerotherapy and a splenectomy for the treatment of portal hypertension. At the age of 42, limb ataxia, dysarthria, and affective disorder were identified. He has suffered from frequent syncopal episodes caused by autonomic nerve failure.

Polymerase chain reaction (PCR) and DNA sequencing

Informed consent was obtained from all patients. Genomic DNA was isolated from the peripheral blood leukocytes of the subjects by the standard method, as previously described (Kimura and Sasazuki 1992). All 21 exons of the gene for WD were amplified by PCR. The PCR amplification conditions and primers used in the present study were all described previously (Thomas et al. 1995; Petrukhin et al. 1994). PCR products were purified with Microcon-100 (Amicon, Beverly, MA, USA), and DNA sequencing was performed using a Thermo Sequenase II dye terminator cycle sequencing kit (Amersham Life Science, Cleveland, OH, USA) as recommended by the supplier. Unincorporated dye-terminator was removed by Centri-Sep Spin Columns (Perkin-Elmer, Applied Biosystems Division, Foster City, CA, USA). Then the reaction mixture was analyzed on an automated sequencer (model 373S; Perkin-Elmer, Applied Biosystems Division).

Results

Mutation analysis

Five different mutations were identified in our current analysis (Table 2). Among them, two (2513delA,

Table 1. Phenotype and genotype of patients with WD and their parents

Patient	Age/Sex (years)	Age of onset (years)	Symptoms	Kayser-Fleischer rings	s-Cp[a]	s-Cu[b]	u-Cu[c]	Genotype
Case 1	16/M	16	Fulminant hepatitis Hemolytic anemia	+	6	46	326	2513delA-2871delC
Case 2	14/M	14	Chronic hepatitis	+	2	33	115	2513delA-2871delC
F1	M	—	—	−	15	59	—	2871delC
M1	F	—	—	−	22	84	—	2513delA
Case 3	38/M	27	Liver cirrhosis, tremor	+	<2.0	10	—	A874V-A874V
Case 4	44/M	22	Liver cirrhosis, dysarthria, affective disorder, autonomic dysfunction	+	<2.0	10	—	R778L-3892delGTC

F1, Father of cases 1 and 2; M1, mother of cases 1 and 2; WD, Wilson disease
[a] Serum ceruloplasmin (normal range, 18–37 mg/dl)
[b] Serum copper (normal range, 78–131 μg/dl)
[c] Urine copper (normal range, 3.3–4.3 μg/day)

Table 2. Mutations of the *ATP7B* gene found in the present study

Base pair	Codon	Mutation	Exon	Predicted effect
G2333T	CGG→CTG	R778L[a,b,c,d,e,f,g]	8	Disrupts Tm4
A2513del	AAG→AxG	2513delA	10	Frameshift
C2621T	GCG→GTG	A874V[e,f,h]	11	Disrupts Td
C2871del	CCC→CCx	2871delC[c,e,i]	13	Frameshift
3892delGTC	GTC→x	3892delGTC	18	Inframe deletion/disrupts ATP hinge

Base pairs and amino acids are numbered according to the published ATG initiation codon (Petrukhin et al. 1994)
[a–i] Show mutations which were previously described
[a] Thomas et al. 1995
[b] Chuang et al. 1996
[c] Nanji et al. 1997
[d] Nakazono et al. 1998
[e] Arashima et al. 1998
[f] Kim et al. 1998
[g] Tsai et al. 1998
[h] Yamaguchi et al. 1998
[i] Okada et al. 1998

3892delGTC) were novel mutations (Fig. 1), while the other three (R778L, A874V, 2871delC) have been reported elsewhere. Of these, four were found to be compound heterozygotes, and the mutation, A874V, was found to be a homozygote (Table 1). The new mutation, 2513delA, would alter the reading frame and result in a truncated polypeptide of 871 amino acid residues. The mutation, 2871delC, would alter the reading frame and result in a truncated polypeptide of 965 amino acid residues, which has been found in a relatively large proportion of Japanese (28.2%) (Okada et al. 1998). These mutations would most likely result in the absence of a protein product or in a shortened functionless protein lacking several essential functional regions, and these two mutations (2513delA, 2871delC) were found in patients with hepatic type WD (Table 1).

In contrast to these mutations, the mutations, A874V and R778L, which occurred in cases 3 and 4, respectively, were missense mutations previously reported in a relatively large number of Japanese patients and were confirmed to be disease-causing mutations. Another new mutation, 3892delGTC, was an inframe deletion and is expected to produce protein lacking Val1298, which disrupts the ATP hinge region. These three mutations (A874V, R778L, and 3892delGTC) were detected in hepato-neurologic type patients as a homozygote or a compound heterozygote.

Polymorphisms

We also identified 16 polymorphisms in the gene for WD: 6 of these (-119CGCCG, V290L, D1407E, 1544-4delG, 1544-2insG, and L722L) were novel, while the other 10 have been described elsewhere (Table 3). Each of these nucleotide changes is considered to be a polymorphism but not a mutation, in accordance with the following criteria: (1) It is found in chromosomes with a defined disease-causing mutation. (2) It is detected in a homozygous state in normal chromosomes of the same population. (3) It does not

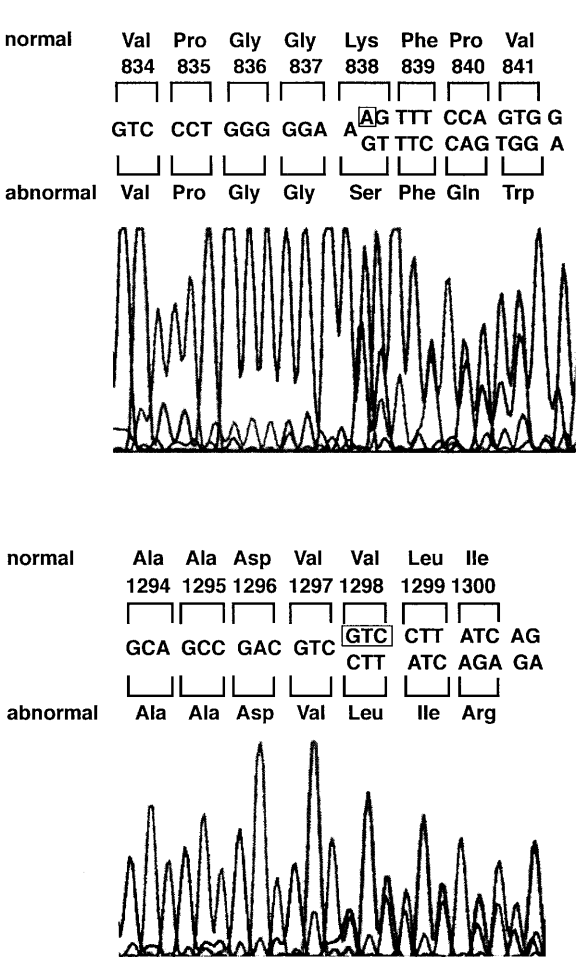

Fig. 1a,b. Sequence analysis of the novel mutations of the *ATP7B* gene. **a** A 1-bp (A) deletion at nucleotide 2513 (codon 838) of exon 10 from cases 1 and 2. The frameshift results in a completely different amino acid sequence from codon 838. **b** A 3-bp (GTC) deletion at nucleotide 3892 (codon 1298) of exon 18 from case 4. The inframe deletion results in a single amino acid (Val) deletion at codon 1298

Table 3. Polymorphisms in *ATP7B* gene found in the present study

Base pair	Polymorphism	Codon	Exon/intron	Evidence
	−75A→C[a,b,c,d,e]		5′-UTR	(1)
	−119delCGCCG		5′-UTR	(1)
C870G	V290L	GTC→GTG	Exon 2	(2)
G1216T	A406S[a,c,d,e,f,g,h,i]	GCT→TCT	Exon 2	(1)
T4221A	D1407E	GAT→GAA	Exon 2	(1)
	1544 − 4delG		Intron 3	(1)
	1544 − 2insG		Intron 3	(1)
C1366G	L456V[a,c,g,h,i]	CTG→GTG	Exon 3	(2)
	1707 + 9insGT		Intron 4	(1)
	1870 − 2delA[j]		Intron 5	(1)
C2166A	L722L	CTG→CTT	Exon 8	(3)
C2310G	L770L[c,j,k]	CTC→CTG	Exon 8	(1)
G2495A	R832K[a,g,h,j,k,l]	AGG→AAG	Exon 10	(1)
A2855G	K952R[a,c,d,g,h,i]	AAA→AGA	Exon 12	(1)
C3419T	A1140V[a,b,c,d,e,g,h,i,j,l]	GCC→GTC	Exon 16	(2)
	3903 + 6 (T→C)[a,d,e,g,h,k]		Intron 18	(2)

Evidence of each polymorphism is classified as follows and indicated in the Table:
(1) It is found in chromosomes with a defined disease-causing mutation
(2) It is detected in a homozygous state in normal chromosomes of the same population
(3) It does not modify the amino acid sequence of the protein product
(4) It results in non-conservative changes in nonessential residues of the protein
UTR, Untranslated region
[a–l] Show previously described polymorphisms
[a] Figus et al. 1995
[b] Shah et al. 1997
[c] Tsai et al. 1998
[d] Yamaguchi et al. 1998
[e] Loudianos et al. 1998
[f] Bull et al. 1993
[g] Thomas et al. 1995
[h] Waldenström et al. 1996
[i] Ha-Hao et al. 1998
[j] Kim et al. 1998
[k] Nanji et al. 1998
[l] Kalinsky et al. 1998

modify the amino acid sequence of the protein product. (4) It results in non-conservative changes in nonessential residues of the protein (Figus et al. 1995).

Discussion

We analyzed the mutation of the *ATP7B* gene on eight WD chromosomes and identified five different mutations (100% of chromosomes examined), of which two were not previously reported. This suggests that the direct sequencing method is an accurate way of analyzing such mutations.

One of the novel mutations, 2513delA, was found in cases 1 and 2, and occurred as a compound heterozygote with the mutation, 2871delC, which is one of the most frequent mutations in Japan; its reported frequency is 28.2% (Okada et al. 1998). The mutation in case 3, A874V, has also been found in Japan. The genotypes of the reported cases of this mutation were all compound heterozygotes. Therefore, our case 3 is considered to be the first reported case of an A874V homozygote. It is important to observe the phenotype of homozygotes, because the mutation-specific phenotype can be assessed only in these patients. In this context, our case 3 indicated that the A874 homozygote phenotype showed a hepato-neurologic type with a relatively late onset.

Another novel mutation found in the present study was the inframe deletion, 3892delGTC, which was found in case 4 as a compound heterozygote with R778L. This R778L mutation was initially found in Chinese patients (Thomas et al. 1995) and is one of the most common mutations known in Asian countries. The frequencies of this mutation have been reported to be 14.6% in Japanese patients (Nanji et al. 1997), 37.5% in Korean patients (Kim et al. 1998), and 11.4%–28.9% in Taiwanese patients (Chuang et al. 1996; Tsai et al. 1998). On the other hand, the R778L mutation has not yet been reported in Caucasian patients.

The tendency of a population-specific mutation in Japanese patients has been reported (Arashima et al. 1998). A sequence analysis in eight exons, ie exons 8, 10, 11, 12, 13, 14, 16, and 18, has been recommended to effectively screen for the mutation. The mutations detected in this study were all included in the above exons, thus indicating this to be a suitable strategy for a mutation analysis of WD in Japanese patients.

Several studies have reported on genotype-phenotype correlations (Thomas et al. 1995; Houwen et al. 1995; Shimizu et al. 1995; Czlonkowska et al. 1997; Shah et al. 1997; Ha-Hao et al. 1998; Kalinsky et al. 1998; Okada et al. 1998). As shown in Table 4, some tendencies regarding

Table 4. Correlations of genotypes with phenotypes in Japanese patients reported in the literature

Genotype	Phenotype	Number of cases
Frameshift mutation		
2871delC (homozygote)	Hepatic (fulminant hepatitis)	1[a]
	Hepato-neurologic	1[a]
2871delC-2513delA	Hepatic (fulminant hepatitis/chronic hepatitis)	2[b]
2874delC (homozygote)	Hepatic	2[c]
	Presymptomatic	1[c]
2874delC-2662delG	Hepatic	1[c]
	Presymptomatic	1[c]
2302insC (homozygote)	Presymptomatic	1[d]
Missense mutation/inframe deletion/exon skipping		
R778L (homozygote)	Neurologic, hepato-neurologic	2[c]
	Presymptomatic	1[c]
1651-5T→G (homozygote)	Neurologic	2[e]
A874V (homozygote)	Hepato-neurologic	1[b]
R778L-3892delGTC	Hepato-neurologic	1[b]

[a] Okada et al. 1998
[b] Present study
[c] Shimizu et al. 1997a
[d] Shimizu et al. 1997b
[e] Shimizu et al. 1995

phenotype-genotype correlations have been observed in Japanese patients; ie, patients with either homozygotes or compound heterozygotes of frameshift mutations which would produce an advanced truncated protein of ATP7B from both alleles show a severe form of hepatic type WD with an early onset; on the other hand, the patients with either a missense mutation, inframe deletion, or exon skipping, which produces less severe changes in the *ATP7B* protein, show a less severe form of neurologic or hepato-neurologic type of late onset. The genotype-phenotype correlation in the present patients was compatible with this hypothesis, as cases 1 and 2, who were compound heterozygotes with frameshift mutations, revealed hepatic manifestation of early onset, while cases 3 and 4, with either missense mutations or inframe deletion, revealed a hepato-neurological manifestation of late onset. In contrast to findings in Japanese patients, analyses of phenotype-genotype correlations in other ethnic populations remain controversial. The most common mutation outside the Japanese population is H1069Q (formerly designated H714Q), which accounts for 22%–31% of the known WD mutations in Europe and America (Tanzi et al. 1993; Thomas et al. 1995) and for 73% in Poland (Czlonkowska et al. 1997). The homozygotes of this H1069Q mutation are associated with a neurologic type of late onset (Houwen et al. 1995; Czlonkowska et al. 1997); however, other reports indicate more divergence in the phenotypes of this genotype (Thomas et al. 1995; Ha-Hao et al. 1998; Ivanova-Smolenskaya et al. 1999). The reason for such differences between the Japanese population and the populations in Europe and America is not clear at present; however, they may be caused by different spectrums of mutations or by environmental factors, eg, dietary copper intake, and the genetic background which modifies the function of *ATP7B* (Kalinsky et al. 1998). Further cases should be accumulated to better elucidate whether any phenotype-genotype correlations and population-specific mutations exist in Wilson disease.

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