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RESEARCH REPORT

Homozygosity for Non-H1069Q Missense Mutations in ATP7B Gene and Early Severe Liver Disease: Report of Two Families and a Meta-analysis

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Abstract Most patients with Wilson's disease (WD) are compound heterozygote, which complicates establishing genotype–phenotype correlations. We identified five patients who presented with early and/or severe hepatic disease who are homozygous for W939C missense mutation on exon 12 of ATP7B. We therefore conducted a meta-analysis to determine the phenotype of patients homozygous for missense or nonsense mutations in all ATP7B exons.

The meta-analysis showed that 69% and 31% of patients are homozygous for H1069Q and non-H1069Q mutations, respectively. Compared to patients with H1069Q, those with non-H1069Q mutations were significantly more likely to have a hepatic phenotype, severe liver disease, a mixed phenotype, and less likely to have a neurologic phenotype. Compared to patients with nonsense mutations, those with non-H1069Q ones were equally likely to present with a hepatic phenotype and to have severe liver disease. Mean age at symptom onset in the non-H1069Q versus the H1069Q group was 15.5 versus 20.5 years ($p < 0.001$).

Our data suggest that mutation W939C and other non-H1069Q missense mutations are associated with early disease onset, a hepatic phenotype, and a high risk of hepatic failure in homozygous patients. Early identification of such patients by genetic screening is important for timely initiation of treatment and prevention of complications.

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Introduction

Wilson's disease (WD) (MIM #277900) is a disorder of copper metabolism caused by mutations in the ATP7B gene, resulting in impaired function of the copper transporter Cu-ATPase and deposition of copper in various organs, particularly the liver and brain (Ala et al. 2007; Ferenci 2004). Clinical presentation of WD is variable. Patients present usually with hepatic, neurologic, or mixed hepatic and neurologic manifestations. Some are asymptomatic at diagnosis (Taly et al. 2007). The onset age of WD can range widely (2–71 years), but liver disease is more often the initial presentation in children and young adults compared to older patients (Ferenci et al. 2007; Manolaki et al. 2009).

WD is characterized by mutational diversity with more than 400 mutations identified thus far, and many of which are population specific. Establishing genotype–phenotype correlations is important for proper patient management, for initiation of early treatment in asymptomatic individuals to prevent certain complications, and for predicting the efficacy of treatment. Furthermore, it enhances understanding the molecular pathogenesis of the disease.

Reported associations between a given mutation and a specific WD phenotype remain preliminary and inconclusive (Liu et al. 2004; Margarit et al. 2005; Panagiotakaki

et al. 2004). Attempts to establish genotype–phenotype correlations in WD have been hampered by several factors including: the small number of patients, the large number of mutations, and the fact that most patients are compound heterozygote making it difficult to ascribe a clinical phenotype to one mutated allele versus the other (Loudianos et al. 1999; Riordan and Williams 2001). Phenotypic diversity occurs within the same family, among the same genotype siblings (Riordan and Williams 2001; Takeshita et al. 2002), and even among monozygotic twins (Fraga et al. 2005; Machin 1996; Kegley et al. 2010). One meta-analysis (Stapelbroek et al. 2004) associated H1069Q with late-onset disease and neurological symptoms in contrast to other studies (Duc et al. 1998; Ivanova-Smolenskaya et al. 1999; Shah et al. 1997) that found no correlation between this mutation and clinical presentation. In addition, findings that nonsense and frameshift mutations are associated with early and severe liver disease (Gromadzka et al. 2005; Merle et al. 2010) were not replicated by others (Angius et al. 1998; Deguti et al. 2004; Okada et al. 2000; Palsson et al. 2001). Missense mutations were presumed to result in milder phenotypes compared to frameshift and nonsense mutations, but this too was not substantiated (Deguti et al. 2004; Firneisz et al. 2002; Loudianos et al. 1999; Shah et al., 1997; Wu et al. 2001). Finally, late-onset neurologic WD can occur without any evidence of liver involvement (Ferenci et al. 2007).

Establishing genotype–phenotype correlations is facilitated by studying patients who are homozygous for specific mutations (Barada et al. 2007, 2010; Thomas et al. 1995). We report here the genotypic and phenotypic profile of five patients from two unrelated Lebanese families who are homozygous for W939C, a missense mutation in exon-12 of ATP7B, and who had early and/or severe liver disease. To elucidate this finding, we conducted a comprehensive meta-analysis that included 448 and 29 patients homozygous for missense and nonsense mutations in the ATP7B exons, respectively. We propose the association of homozygous missense non-H1069Q mutations with early and severe hepatic involvement.

Materials and Methods

Twelve subjects from two Lebanese families were studied (Fig. 1): Family-T ($n = 5$, T1–T5) and Family-B ($n = 7$, B1–B6, B8). Three members of Family-T [2 in USA, 1 at American University of Beirut Medical Center (AUBMC)] and two members of Family-B [1 at AUBMC, 1 elsewhere] were diagnosed with WD. Evaluation of patients included history, physical exam, slit-lamp examination, abdominal ultrasound, liver function tests, serum copper, ceruloplasmin and 24 h urinary-Cu levels. Subsequently, DNA screening for mutations or single-nucleotide polymorphisms (SNPs) was performed. DNA extraction, amplification of the various exons by PCR, and sequencing methods were carried on as described before (Barada et al. 2010) using blood samples from members of Family-B and -T. Subjects or their guardian signed a consent form (protocol # BioCh.JU.01) approved by the Institutional Review Board (IRB) at AUB-MC.

Meta-analysis: Phenotypes of Patients Homozygous for Missense and Nonsense Mutations in ATP7B Gene

We did a comprehensive literature review of all the articles mentioned in the University of Alberta database and retrieved all articles published in PubMed and Medline between 1993 and 2010 using the following index terms: Wilson disease, mutation, phenotype, and genotype. We included all articles in which the phenotypes of patients homozygous for missense or nonsense mutations were clearly stated. We considered patients to have severe liver disease if they had cirrhosis or fulminant hepatic failure.

Inclusion and Exclusion Criteria

To establish associations between genotype and phenotype, the analysis included only patients in whom the phenotype was clearly stated in the published articles and who are homozygous for missense or nonsense mutations—including the five patients presented in this study. Patients whose phenotype was not clearly stated as hepatic, neurologic, mixed or asymptomatic were excluded. Patients were considered to have severe liver disease if it was clearly indicated that they have cirrhosis or fulminant hepatic failure. All other patients (asymptomatic, neurologic, mixed, and other hepatic presentations) were considered as nonsevere. For comparing age at presentation among the various groups, we used the individual patient age when provided or repeated the mean or median age provided by the authors as appropriate. Patients were excluded from the age analysis if neither individual nor averaged age data were available.

Statistical Analysis

Data on our patients were combined with data abstracted from the literature. The Chi square test or Fisher Exact Test was used to compare the prevalence rates among the cohorts of (a) hepatic versus nonhepatic phenotype, and (b) severe versus nonsevere hepatic phenotype as defined above. Patient cohort comparisons included: (1) homozygous for non-H1069Q missense mutations anywhere along ATP7B versus homozygous for H1069Q, (2) homozygous

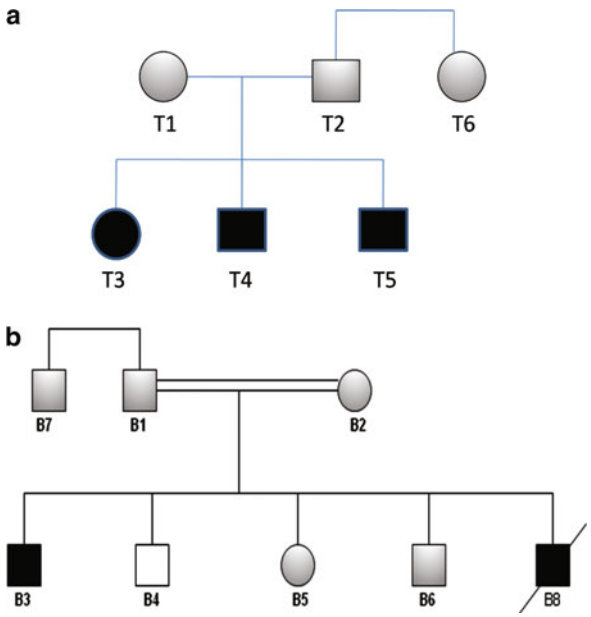

Fig. 1 (**a**) Pedigree of family-T, which consists of six members with T3, T4, and T5 diagnosed with WD. (**b**) Pedigree of family-B, which consists of seven members with B3 and B8 diagnosed with WD. Patients were homozygous for W939C, whereas parents were heterozygous. B8 passed away of fulminant hepatic failure. B4 had a normal sequence

missense (Any) versus homozygous nonsense mutations, and (3) homozygous for non-H1069Q missense versus homozygous nonsense mutations. Age comparisons among the same patient subcohorts were done using the two-tailed unpaired *t*-test or Mann–Whitney rank sum test on median age as appropriate. Determination of significance was set at the 5% level. All analyses were done using SigmaPlot version 11 (2008; Systat Software Inc., San Jose, CA).

Results

The clinical profile of Family-T and Family-B patients is shown in Table 1. Family-T consists of five-members (Fig. 1a). The parents are not consanguineous. Three members (T3, T4 and T5) have WD, all were asymptomatic at diagnosis. Family-B consists of seven-members (Fig. 1b). The parents are first-degree relatives. B3 has WD and B8 died at the age of 5 years of fulminant hepatic failure due to WD. Both B3 and B8 had severe liver involvement based on clinical, laboratory, and radiological criteria at the ages of 5 and 8 years, respectively. A presumptive diagnosis of WD was made for B8 at the age of 5 years based on a very low serum ceruloplasmin level, a borderline low serum Cu, and a positive family history. He developed fulminant liver failure and died of severe gastrointestinal bleeding. Unaffected members of both families had a full evaluation and were asymptomatic and their physical exam, serum ceruloplasmin, serum copper, and 24 h urine Cu were all normal.

Mutation Analysis

Patients, T3, T4, T5, and B3 were homozygous for the disease-causing mutation in exon-12 (W939C) Unaffected members T1, T2, B1, B2, B5, and B6 were heterozygous for this mutation. Patient B8 passed away before any genotypic analysis was done. Furthermore, all patients were homozygous for the following SNPs: K834R (E10), R952K (E12), A1003A (E13), and V1140A (E16). Members of Family-T, but not Family-B, were also homozygous for S1166S.

Meta-analysis Findings

The meta-analysis included a total of 448 patients with clearly stated phenotype who were homozygous for missense mutations along ATP7B, 311 with H1069Q and 137 with non-H1069Q mutations (Table 2). It also included 29 patients who are homozygous for nonsense mutations anywhere along ATP7B. Hepatic phenotype was reported in 85 patients (62%) of the non-H1069Q group compared to 115 (37%) in the H1069Q group ($p < 0.001$). Furthermore, severe liver disease occurred in 24.8% of the non-H1069Q versus 8.4% in the H1069Q group ($p < 0.001$). The mixed phenotype was also more common in the non-H1069Q group (12.4 versus 6.1%, $p = 0.038$). Conversely, neurologic phenotype was much more likely to occur in the H1069Q group (54.0 versus 14.6%, $p < 0.001$). There were 29 patients homozygous for nonsense mutations in

Table 1 Clinical and biochemical profile of five newly diagnosed Lebanese WD Patients, homozygous for W939C mutation

	T3	T4	T5	B3	B8 (deceased)
Year of birth	1998	2001	2006	1992	2002
Age of symptoms onset	Asymptomatic	Asymptomatic	Asymptomatic	8	5
Age at diagnosis	7 (incidental)	8 (by screening)	3 (by screening)	13	5
GI manifestations	Asymptomatic transaminitis	Asymptomatic transaminitis	Asymptomatic transaminitis	At age 8: hepatosplenomegaly cirrhosis, ascites	Jaundice, abdominal distention, hematemesis, shifting dullness, hepatomegaly
Neurological manifestations	None	None	None	Drooping of the jaw, hypersalivation, slurred speech, narrow-based gait, intention tremors	Hepatic encephalopathy
Kayser Fleischer ring	Absent	Absent	Absent	Present	Absent
Serum copper	5	6	9	2	72
Serum ceruloplasmin	<0.02	<0.02	<0.02	<0.0211	0.04
24-h-urine copper	77.6	20	41.5	744	Not done
Alkaline phosphatase	288	286	257	191	131
GGT	89	23	26	230	21
SGPT	248	152	59	25	74.1
SGOT	112	93	54	33	150
Bilirubin T/D	0.6/0.2	0.8/0.2	0.7/<0.1	0.8/0.3	38.06/21.44
PT/INR	12.9/1.10	13.2/1.10	11.4/1.00	14.3/1.2	>8.31/>120
Albumin	47	48	44	40	34.08
Globulin	29	31	21	26	20
Ultrasound of abdomen	Hepatomegaly, echogenic liver	Increase in the liver echotexture, irregular contour, cirrhosis	Increase in the liver echotexture, irregular contour, cirrhosis	Hepatosplenomegaly (chronic liver disease or cirrhosis) Small amount of ascites	Mild-to-moderate ascites
MRI of brain	Normal	Normal	Not done	Bilateral symmetrical areas of abnormal signals in the putamen, thalami, caudate, midbrain, superior cerebellar hemispheres and dentate nuclei	Not done
Liver histopathology	Chronic liver disease, bridging, fibrosis, macro-vesicular fatty changes	Fatty change, portal fibrosis	Not done	Not done	Not done

Normal ranges of: Serum ceruloplasmin: 0.20–0.60 g/L; Serum Cu is 70–150 μg/dL; Urine Cu (μg/24 h): 15–50 μg/24 h

Table 2 Phenotypes of patients homozygous for missense mutations in the WD gene

Exon	Mutation	# Hepatic (%)	# Neurologic (%)	# Mixed (%)	# Asymptomatic (%)	References
E5	R616Q	1 (100%)	–	–	–	Santhosh et al. (2006)
E7	P690L	1 (100%)	–	–	–	Margarit et al. (2005)
	G691R	2 (40%)	–	–	3 (60%)	Barada et al. (2007)
E8	R778L	20 (71.4%)	5 (17.9%)	–	3 (10.7%)	Butler et al. (2001), Okada et al. (2000), Thomas et al. (1995), Wu et al. (2001), Yoo (2002)
	L708P	3 (25%)	6 (50%)	–	3 (25%)	Garcia-Villarreal et al. (2000)
	G710A	1 (100%)	–	–	–	Duc et al. (1998)
	G710S	1 (50%)	1 (50%)	–	–	Waldenstrom et al. (1996)
	L708P	2 (50%)	–	2 (50%)	–	Deguti et al. (2004)
	D765N	–	–	1 (100%)	–	Deguti et al. (2004)
	P768L	1 (100%)	–	–	–	Santhosh et al. (2006)
E10	I857T	–	–	1 (100%)	–	Folhoffer et al. (2007)
E11	G875R	3 (100%)	–	–	–	Santhosh et al. (2008)
	A874V	–	–	1 (100%)	–	Kusuda et al. (2000)
E12	G943S	–	1 (100%)	–	–	Thomas et al. (1995)
	W939C	4 (80%)	–	1 (20%)	–	Our study
E13	R969Q	1 (100%)	–	–	–	Santhosh et al. (2006)
	R969W	4 (57%)	–	–	3 (43%)	Panagiotakaki et al. (2004)
	P992L	1 (33%)	2 (67%)	–	–	Gu et al. (2003), Wu et al. (2006)
	A1003V	1 (100%)	–	–	–	Santhosh et al. (2006)
	K1010R	3 (75%)	–	–	1 (25%)	Santhosh et al. (2006), Santhosh et al. (2008)
E14	G1061E	2 (100%)	–	–	–	Margarit et al. (2005), Santhosh, et al. (2006)
	A1065P	1 (100%)	–	–	–	Brage et al. (2007)
	H1069Q	115 (37%)	168 (54%)	19 (6%)	9 (3%)	Brage et al. (2007), Butler et al. (2001), Caca et al. (2001), Caprai et al. (2006), Curtis et al. (1999), Duc et al. (1998), Ferenci et al. (2007), Firneisz et al. (2002), Houwen et al. (1995), Kucinskas et al. (2008), Loudianos et al. (2003), Maier-Dobersberger et al. (1997), Panagiotakaki et al. (2004), Shah et al. (1997), Stapelbroek et al. (2004), Tarnacka et al. (2000), Thomas et al. (1995), Vrabelova et al. (2005)
E15	G1101R	1 (50%)	–	–	1 (50%)	Thomas et al. (1995)
	I1102T	2 (100%)	–	–	–	Butler et al. (2001), Thomas et al. (1995)
	C1104F	1 (100%)	–	–	–	Loudianos et al. (1999)
	F1094L	–	–	1 (100%)	–	Deguti et al. (2004)
E16	I1148T	2 (100%)	–	–	–	Panagiotakaki et al. (2004)
E17	T1232P	1 (100%)	–	–	–	Margarit et al. (2005)
E18	V1262F	1 (100%)	–	–	–	Loudianos et al. (1999)
	G1266K	2 (40%)	2 (40%)	–	1 (20%)	Tarnacka et al. (2000), Thomas et al. (1995)
	N1270T	1 (50%)	–	1 (50%)	–	Santhosh et al. (2006), Yoo (2002)
	N1270S	2 (50%)	–	2 (50%)	–	Barada et al. (2010), Santhosh et al. (2006)
	P1273L	2 (100%)	–	–	–	Barada et al. (2010)
E19	G1341S	–	2 (66%)	1 (34%)	–	Santhosh et al. (2006), Santhosh et al. (2008)
E20	S1363F	–	1 (100%)	–	–	Loudianos et al. (1999)
–[a]	–	18 (75%)	–	6 (25%)	–	Abdelghaffar et al. (2008)

Note: No patients with homozygous missense mutations in Exons: 1–4, 6, and 9 with a clearly defined phenotype were reported

[a] Nineteen different missense mutations were reported in 24 patients (Abdelghaffar et al. 2008)

Table 3 Prevalence of various phenotypes in patients homozygous for missense or nonsense mutations in the ATP7B gene

Disease		Homozygous missense mutations (ATP7B)				Nonsense	
Presentation		H1069Q *N* (%)	Non-H1069Q *N* (%)	*P* value	Overall *N* (%)	Mutations[a] *N* (%)	*P* value
No. of patients		311	137		448	29	
Hepatic only[b]	Yes	115 (37.0%)	85 (62.0%)	<0.001	200 (44.6%)	13 (44.8%)	0.86
	No	196 (63.0%)	52 (38.0%)		248 (55.4%)	16 (55.2%)	
Severe hepatic[b,c]	Yes	24 (8.4%)	34 (24.8%)	<0.001	58 (13.7%)	3 (10.3%)	0.849
	No	261 (91.6%)	103 (75.2%)		364 (86.3%)	26 (89.7%)	
Neurologic only[b]	Yes	168 (54.0%)	20 (14.6%)	<0.001	188 (42.0%)	7 (24.1%)	0.09
	No	143 (46%)	117 (85.4%)		260 (58.0%)	22 (75.9%)	
Mixed	Yes	19 (6.1%)	17 (12.4%)	0.038	36 (8.0%)	9 (31.0%)	<0.001
	No	292 (93.9%)	120 (87.6%)		412 (92.0%)	20 (69.0%)	
Asymptomatic	Yes	9 (2.9%)	13 (9.5%)	0.006	22 (4.9%)	N/A	
	No	302 (97.1%)	(90.5%)		426 (95.1%)	N/A	

[a] References: Abdelghaffar et al. (2008), Folhoffer et al. (2007), Gupta et al. (2005), Prella et al. (2001), Santhosh et al. (2006), Waldenstrom et al. (1996), Deguti et al. (2004), Thomas et al. (1995), Panagiotakaki et al. (2004)

[b] Hepatic presentation ($p = 0.132$) and severity ($p = 0.145$) did not differ significantly for non-H1069Q versus Non-sense mutations, but this may be due to small number of patients

[c] Severity data was unavailable in 26 patients and were excluded from analysis

whom the phenotype could be clearly identified. Of these, 13 (44.8%) had a hepatic phenotype and 3 (10.3%) had severe liver disease (Table 3). There was no significant difference in the prevalence of hepatic phenotype, severe liver disease, or neurologic phenotype between patients with missense and those with nonsense mutations. Age at onset of symptoms was available for 356 of the 448 (79.5%) patients that are homozygous for missense mutations, and it was significantly greater for H1069Q ($n = 293$; 20.5 years) versus non-H1069Q ($n = 63$; 15.1 years) mutations ($p < 0.001$). Mean onset age for non-H1069Q mutations was also greater than those with nonsense mutations ($n = 8$; 10.8 years), yet this difference only approached significance ($p = 0.068$) possibly because of the limited onset age data among nonsense mutation patients.

Discussion

We report in this paper a missense mutation (W939C) that, in the homozygous state, was associated with early and/or severe hepatic disease in five WD patients. Although the W939C mutation was reported before in a single patient in the heterozygous state (Folhoffer et al. 2007), this is the first study to describe the clinical phenotype of a group of patients with this mutation in the homozygous state. The primary findings of the accompanying meta-analysis of all reported homozygous mutations in ATP7B are: (1) patients who are homozygous for non-H1069Q missense mutations are more likely to develop symptoms at a younger age, to have a hepatic phenotype, and to have severe liver disease on presentation than their H1069Q counterparts, (2) the phenotype–genotype analysis does not lend support to the notion that patients with nonsense mutations have more severe disease compared to missense mutation patients, and (3) patients who are homozygous for H1069Q mutations are more likely to present with later and neurologic manifestations as previously reported (Stapelbroek et al. 2004; Gromadzka et al. 2006; Ferenci et al. 2007).

More than 400 mutations have been described in WD, and missense ones are the most common. Multiple difficulties in establishing clear and convincing genotype–phenotype correlations in WD have been described (Curtis et al. 1999; Kalinsky et al. 1998; Kegley et al. 2010; Margarit et al. 2005; Shah et al. 1997). To overcome them, others (Thomas et al. 1995) and we have proposed (Barada et al. 2010): (1) conducting family studies since their members are more likely to share the same genetic and environmental factors, (2) studying homogenous populations with high rates of consanguinity, which would increase the chance of identifying homozygous patients. Such approach facilitates establishing associations between a phenotype and a given mutation.

The parents in the two-described families are of the same ethnicity, and in one family they were consanguineous. All

five WD patients had liver disease with evidence of hepatocellular injury, fibrosis or cirrhosis as demonstrated by laboratory tests, imaging or liver biopsy at a very young age. Three patients were asymptomatic on presentation, but had biochemical evidence of hepatitis and sonographic evidence of cirrhosis. However, on liver biopsy, patients T3 and T4 had fibrosis and fatty change but no frank cirrhosis. This discrepancy is explained by the fact that the liver biopsies were done 3 years before the abdominal ultrasounds revealing cirrhosis. In the case of T3, T4, T5, and B3, the diagnosis was unequivocal and based on clinical, biochemical, and radiologic findings, in addition to the genetic testing revealing that all four patients were homozygous for the missense mutation in exon-12. B8, however, had a presumptive diagnosis of WD presenting as fulminant hepatitis based on a very low serum ceruloplasmin level, a borderline low serum copper level, and a family history of WD.

Patients with WD may present with neurological manifestations without ever experiencing liver disease, as demonstrated by normal liver tests, imaging and histopathology (Ferenci et al. 2007; Horslen and Hahn 2010). Thus, the course of WD may either start with hepatic or with isolated neurological manifestations. The disease may be mild, severe, or life threatening depending on the ATP7B mutation and other genetic and environmental factors. Our meta-analysis suggests that about 62% of patients homozygous for non-H1069Q mutations present with a hepatic phenotype, and about 24.8% have severe disease, i.e., cirrhosis or fulminant hepatic failure. This diverges with other reports (Duc et al. 1998; Ivanova-Smolenskaya et al. 1999; Shah et al. 1997; Takeshita et al. 2002) because only patients homozygous for missense mutations were considered. However, some non-H1069Q mutations may be associated with neurologic manifestations in the homozygous state, and this may not be statistically apparent due to the small number of patients.

Assigning a specific phenotype to a specific mutation helps predict the pattern of disease progression, the approximate age of symptom onset, and facilitates monitoring the response to therapy. The missense mutation that is reported in this article is associated with early and/or severe liver disease that could lead to early liver failure and death if left untreated. If treated, however, those manifestations may be prevented like in Family-T patients. Hence, it is important to initiate treatment directly at genetic diagnosis in patients homozygous for this mutation and to offer genetic screening to all their family members.

Our findings, in part, confirm and expand those of Stapelbroek et al. (2004). However, we differ from them in several ways: (1) our analysis was restricted to patients homozygous for specific mutations; (2) we compared patients homozygous for H1069Q (common in Europe but rare in the Arab World) to patients homozygous for non-H1069Q mutations reported in the Arab World and elsewhere; (3) we addressed acute and chronic hepatic failure on presentation which is of obvious clinical importance; and (4) we compared patients with missense and nonsense mutations.

There are limitations to our study. The first is the small number of patients with the identified W939C mutation in the homozygous state. The second is that our analysis of the literature was restricted to patients whose phenotype was clearly identified. The third is that the number of patients who are homozygous for missense and nonsense mutations at specific exons is relatively small, rendering exon or mutation specific statistical analysis inapplicable. The relatively small number of WD patients who are homozygous for nonsense mutations limits the statistical power of comparisons with missense counterparts, and hence negative findings or lack of significance must be interpreted with caution. Finally, the non-H1069Q group in our study is a heterogeneous group with missense mutations in various exons of ATP7B. Studies involving larger numbers of patients who are homozygous for missense mutations at specific exons may clarify further genotype/phenotype correlations.

Conclusions

The mutation W939C and other non-H1069Q missense mutations in homozygous patients are associated with early disease onset, a hepatic phenotype, and a high risk of hepatic failure on presentation. Early identification of such affected individuals via genetic screening is important for timely initiation of treatment and prevention of sequelae.

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Competing Interest

The authors declare no competing interest

Take-Home Message (Synopsis)

Mutation W939C and other non-H1069Q missense mutations are associated with early disease onset, a hepatic phenotype, and a high risk of hepatic failure in homozygous patients.

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