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Review

Recent advance in the molecular genetics of Wilson disease and hereditary hemochromatosis

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ABSTRACT

Metabolic liver diseases such as Wilson disease (WD) and hereditary hemochromatosis (HH) possess complicated pathogenesis and typical hereditary characteristics with the hallmarks of a deficiency in metal metabolism. Mutations in genes encoding ATPase, Cu + transporting, beta polypeptide (*ATP7B*) and hemochromatosis (*HFE*) or several non-*HF*E genes are considered to be causative for WD and HH, respectively. Although the identification of novel mutations in *ATP7B* for WD and *HFE* or the non-*HFE* genes for HH has increased, especially with the application of whole genome sequencing technology in recent years, the biological function of the identified mutations, as well as genotype–phenotype correlations remain to be explored. Further analysis of the causative gene mutation would be critical to clarify the mechanisms underlying specific disease phenotypes. In this review, we therefore summarize the recent advances in the molecular genetics of WD and HH including the updated mutation spectrums and the correlation between genotype and phenotype, with an emphasis on biological functional studies of the individual mutations identified in WD and HH. The weakness of the current functional studies and analysis for the clinical association of the individual mutation was also discussed. These works are essential for the understanding of the association between genotypes and phenotypes of these inherited metabolic liver diseases.

Contents

Abbreviations: WD, Wilson disease; HH, Hereditary hemochromatosis; TGN, trans-Golgi network; ATP7B, ATPase; Cu + transporting, beta polypeptide; *HFE*, hemochromatosis; *HJV*, hemojuvelin; *HAMP*, hepcidin antimicrobial peptide; *TFR2*, transferrin receptor 2; *SLC40A1*, solute carrier family 40 member 1.

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1. Introduction

The liver is an important organ that participates in most metabolic pathways including those involving lipids, carbohydrates, amino acids, enzymes, and metallic elements. Liver dysfunction is associated with numerous inherited metabolic diseases, most of which are autosomal recessive disorders with low morbidities such as Wilson disease (WD), hereditary hemochromatosis (HH), α1-antitrypsin deficiency, and hyperlipidemia (Taddei et al., 2008).

WD and HH constitute an important type of inherited metabolic liver disease, involving a deficiency of metal metabolism. They are characterized by the abnormal deposition of copper (WD) or iron (HH) in several organs, but primarily in the liver, which causes its dysfunction (Bacon et al., 2011; EASL, 2012). The treatment of WD and HH includes the use of copper chelating agents or phlebotomy, respectively. The absence or delay in treatment for these disorders has been shown to cause death from severe liver disease or disorders involving other organs (EASL, 2012; Bacon et al., 2011).

Early diagnosis and treatment initiation are associated with an excellent prognosis. Mutations in genes encoding ATPase, Cu + transporting, beta polypeptide (*ATP7B*) or hemochromatosis (*HFE*) have been demonstrated to have a pathogenic role in WD and HH, and may serve as potential biomarkers for early diagnosis. More and more novel mutations in *ATP7B* and HH-related genes have been identified in recent years (Taddei et al., 2008; EASL, 2012; Bacon et al., 2011). However, whether the mutations are pathogenic with an individual disease phenotypes remain unclear or controversial, suggesting the importance of biological functional studies as well as the analyses of genotype−phenotype correlations in a large cohort of cases with full clinical information.

In the current review, we summarize the recent advances regarding the updated mutation spectrum of these genes and the correlation between genotype and phenotype. We place particular emphasis on functional studies of individual mutations, which are essential to understand the association between genotype and phenotype.

2. WD

2.1. Epidemiology, clinical features, diagnosis, and etiology

WD, also called hepatolenticular degeneration, is a monogenic autosomal recessive disease accompanied by lethal chronic liver disease or neurological disease, with a morbidity of 1:30,000 worldwide (EASL, 2012). Its manifestations vary among different patients, but include hepatic dysfunctions ranging from mild abnormalities to acute or chronic hepatitis, cirrhosis, or even fulminant hepatitis, as well as neurological disorders involving Parkinson-like or neuropsychiatric symptoms. Copper deposition in the cornea results in the appearance of a rusty brown Kayser–-Fleischer ring, although this is not specific for diagnosis (EASL, 2012). The age of onset of WD ranges from infancy to old age, with the youngest reported case being an 8-month-old Chinese boy presenting with elevated liver enzymes (Abuduxikuer, 2015). According to the 2012 EASL clinical practice guidelines there is about 3% patients present beyond the fourth decade, and the oldest patients diagnosed were in their eighth decade (EASL, 2012).

The diagnosis of WD is based on WD score system comprising clinical, histologic and biochemical features, and *ATP7B* mutation or the combination with follow-up results (EASL, 2012). A score ≥4 indicates that WD is highly likely, while a score of 2 or 3 indicates that diagnosis is probable and further investigations are needed, and a score of 0 or 1 indicates the disease is unlikely (EASL, 2012). In a recent study, hepatic copper content of 209 μg/g dry wt. was demonstrated better than 250 μg/g dry wt. for the diagnosis of WD (Yang et al., 2015). Genetic mutations in *ATP7B*, which encodes a copper-transporting P-type ATPase, are considered to be causative of WD (Bull et al., 1993).

ATP7B is mainly localized in the trans-Golgi network (TGN) of hepatocytes, but redistributes to an intracellular, vesicular compartment upon increased copper levels, and recycles back to the TGN when copper is removed (Schaefer et al., 1999a), and *ATP7B* mutations may lead to the incorrect localization of ATP7B to the endoplasmic reticulum (ER) (Huster et al., 2003). This can disrupt the copper transport function of ATP7B, leading to excess copper accumulation and hepatic injury (Polishchuk et al., 2014).

2.2. Updates to the ATP7B mutation spectrum

To date, more than 500 *ATP7B* mutations have been identified (Wilson's disease mutation database), and were detected in 72%–90% of alleles in patients with WD (Lee et al., 2011). Most of these are missense point mutations of low frequency that are distributed throughout the 21 exons. The mutation pattern varies among different countries, with distinct hotspots identified in Asian and European populations. The distribution of these mutations is shown in Table 1 and Fig. 1.

In Asia, p.Arg778Leu (c.2333G > T exon 8) has been identified as the most common *ATP7B* mutation, with a frequency of 10.52% in Thailand (Panichareon et al., 2011), and similar patterns in other Asian countries. In a recent study of WD cases from southern China, *ATP7B* mutations were mainly found in exon 8 (23.30%) and exon 16 (12.14%), with the top three mutations being Arg778Leu (18.93%), Ile1148Thr (8.74%), and Pro992Leu (4.37%) (Wei et al., 2014). This is consistent with a previous study from eastern China in which the top three mutations identified in WD cases were p.Arg778Leu (31.9%), p.Pro992Leu (11.2%), and p.Ala874Val (5.17%) (Li et al., 2011). In Hong Kong and Tai Wan, the Arg778Leu accounts for 17.3% (Mak et al., 2008) and 29.63% (Wan et al., 2010) of reported *ATP7B* mutation, respectively. A systematic literature review of 345 Chinese cases also showed the most common *ATP7B* mutations to be located in exons 8, 13, 12, and 16, which together account for 74.0% (Li et al., 2011). The most frequent *ATP7B* mutations were p.Arg778Leu and p.Pro992Leu, which account for 50.43% of all reported *ATP7B* alleles (Li et al., 2011). Similarly, in cases from Korea, p.Arg778Leu having an allele frequency of 39.2% (Park et al., 2007). This contrasts with Japan, where Shimizu et al. revealed that the most frequent of 13 mutations in 23 Japanese WD cases were 2874delC (exon 13, 30%) and Arg778Leu (exon 8, 25%) (Shimizu et al., 1999).

Distinct from the mutations detected in Asian WD cases, p.His1069Gln (c.3207C > A) was confirmed as the most frequent mutation in European countries such as Romanian and France (Iacob et al., 2012; Bost et al., 2012). Recently, Coffey et al. found

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