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Editorial note:

Wilson disease (WD) is a classic inherited metabolic disease of copper metabolism. It is well known for its characteristic Kayser-Fleischer ring, very low serum caeruloplasmin level and the diverse spectrum of clinical presentations. However, the pathogenesis of WD remained a mystery until the discovery of the responsible gene ATP7B in 1993. In the current issue of Topical Update, Lam and Mak gave a concise overview of the function of ATP7B protein, the clinical application of ATP7B genetic testing and the common ATP7B mutations among local population.

Any feedback and suggestions could be directed to Dr Liz YP Yuen (email: yuenyp@ha.org.hk) of the Education Committee, the Hong Kong College of Pathologists. Opinions expressed are those of the authors or named individual, and are not necessarily those of the Hong Kong College of Pathologists.

Diagnosing Wilson disease in the post-genomic era

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Wilson disease (WD) (MIM # 277900) is an autosomal recessive disorder of copper transport. Clinical manifestations of WD vary widely. The age of onset ranges from three to more than 50 years of age. The initial onset of symptoms can be hepatic, neurological, psychiatric or as an acute haemolytic crisis. The prevalence of WD has been estimated to be approximately 1 in 30,000 in the Caucasian population. Although the prevalence of WD in the Hong Kong Chinese has not been investigated, based on our local experiences, WD is common and is the most common inherited liver disease in Hong Kong. In addition, investigators in Japan have suggested that the prevalence of WD in Asians might be higher than that reported in the U.S. and Europe.

In 1993, the gene responsible for WD was identified, and the gene product was predicted to be a copper binding P-type adenosine triphosphatase. The *ATP7B* gene, which consists of 21 exons, spans a genomic region of about 80 kb and encodes a protein of 1465 amino acids. ATP7B is expressed primarily in the liver and kidney. The protein plays a dual function in the hepatocytes. One role is biosynthetic, delivering

copper to apocaeruloplasmin within the Golgi network. The other role of ATP7B is to transport excess copper out of the cell and into the bile canaliculus for subsequent excretion from the body with bile. ATP7B is localized in the trans-Golgi network of hepatocytes under low copper conditions, redistributes to cytoplasmic vesicles when cells are exposed to elevated copper levels, and then recycles back to the trans-Golgi network when copper is removed. Therefore, an *ATP7B* mutant will result in a reduction in the rate of incorporation of copper into apocaeruloplasmin or a reduction in biliary excretion of copper, or both. For example, a WD mutant protein, R778L, has recently been shown to be extensively mislocalized, presumably to the endoplasmic reticulum. Defective biliary excretion leads to accumulation of copper in the liver with progressive liver damage and subsequent copper overflow to the brain, causing loss of coordination and involuntary moments. Deposition in the cornea produces Kayser-Fleischer rings, and accumulation in the other sites causes renal tubular damage, cardiomyopathy, hypoparathyroidism osteoporosis, and arthropathy, etc.

The prognosis for WD patients is excellent with early treatment with D-penicillamine, trientine, or zinc salts. Early detection, monitoring, and treatment of presymptomatic patients are critical to prevent irreversible damages to the liver and brain damage. Biochemical parameters (e.g. low level of serum caeruloplasmin concentration and elevated 24-hour urine copper level) and clinical signs and symptoms (e.g. Kayser-Fleischer rings) are not specific enough for effective diagnosis of all affected individuals. In addition, the clinical and laboratory parameters are not sufficient to exclude the diagnosis of WD in patients with liver disease of unknown origin. Direct detection of the *ATP7B* mutations causing WD will eliminate these problems. Direct mutation detection is particularly important and useful in the diagnosis of presymptomatic family members because it is very difficult to distinguish presymptomatic patients from heterozygotes based on biochemical parameters.

The most frequent *ATP7B* mutation in Caucasian patients is H1069Q, which is found in 28%-38% of all alleles. The next most frequent mutation is G1267K, which is found in 10%. These two mutations have so far not been detected in Asian WD patients. This finding reveals that the mutation spectrum of the *ATP7B* gene shows a population-dependent distribution. We were the first group to study the *ATP7B* gene in Hong Kong Chinese. Sixty-four WD patients from 54 unrelated Chinese families were recruited. Ten of the 64 patients were presymptomatic family members. The median age at presentation was 18 years old (range 4 – 50). We identified 38 different mutations in the 54 probands (Fig. 1). Interestingly, 14 mutations are novel. Over 50% of the mutations are located in 3 of 21 exons of the *ATP7B* gene – exons 8, 13, and 16. The mutations, R778L, P992L, and I1148T are the three most common mutations detected in this study. These 3 mutations probably represent the most prevalent *ATP7B* mutations in Hong Kong Chinese WD patients (Fig. 2).

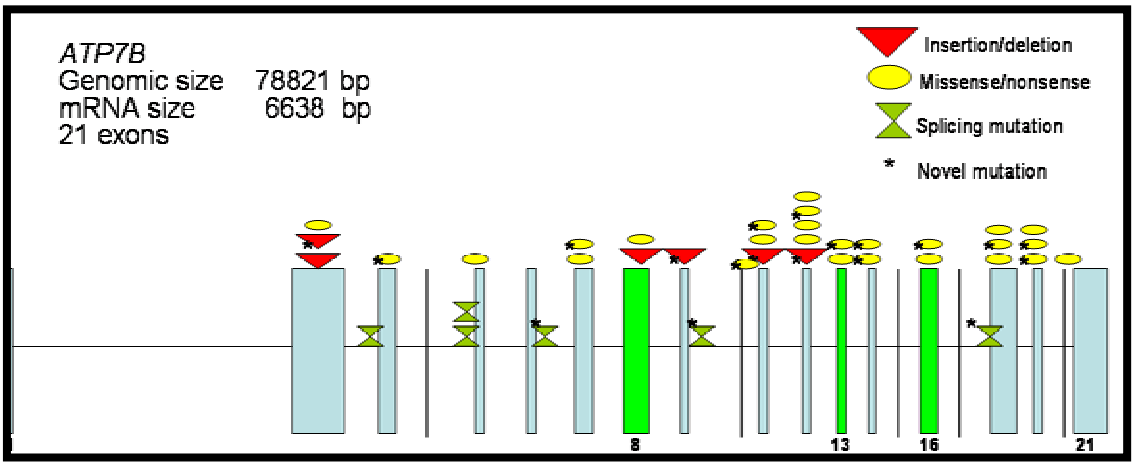

Figure 1. Distribution of the 38 mutations in the *ATP7B* gene.

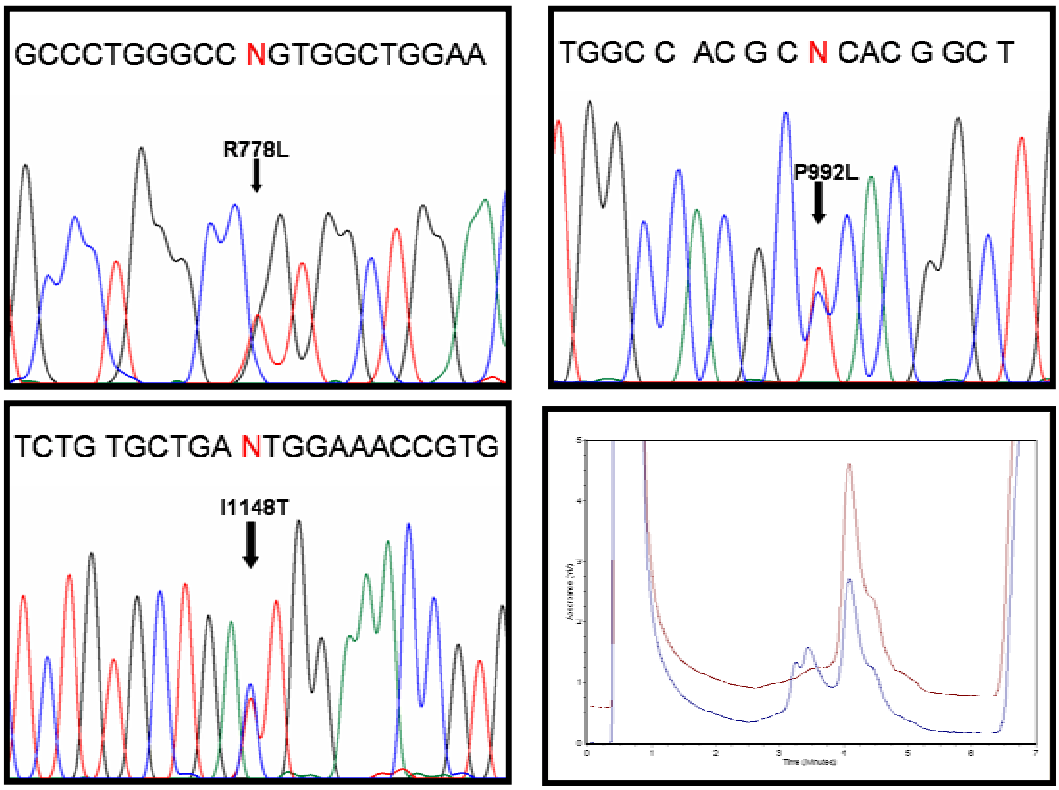

Figure 2: Common *ATP7B* mutations. Upper Left: R778L. Upper Right: P992L. Lower Left: I1148T (arrows). Lower Right: denaturing high performance chromatogram of exon 13: red: wild type DNA; blue: P992L heterozygous.