Wilson disease (WD) represents a monogenic disease resulting in copper accumulation within tissues. Incidence is estimated to be approximately 1:30,000. Symptoms include acute and chronic liver disease, hemolysis, and neurodegenerative and psychiatric symptoms (1). The first symptom may be acute liver failure. Death or liver transplantation in WD is common. The European Liver Transplant Registry recorded 706 liver transplantations for WD from 1 January 1988 to 31 December 2005, underlining the relevance of this disease burden. Because symptoms and disease course are variable, diagnosis can be difficult. Effective treatment for WD such as copper chelating drugs and zinc is available, which usually prevents disease progression. Therefore, a simple, rapid and diagnostic test is required for WD, ideally to identify patients before symptoms appear. First symptoms have been reported in patients as young as 2 years of age (2,3). Thus screening tests for WD at least at the age of 2 years would be appropriate. Penetrance of disease is expected to be 100%. Therefore, treatment should be initiated in affected children already at this age to prevent disease burden.

There is no single test available to exclude WD, especially in young children. Typical diagnostic tests, such as copper concentration in serum and urine and ceruloplasmin concentration in serum, are often normal at this young age and characteristic Kayser-Fleischer-rings are not visible in the eyes on slit-lamp examination. Genetic testing is therefore the most promising tool to screen for WD. Screening of 1st-degree relatives of index patients is currently the best option to identify presymptomatic individuals, but screening tests for the general population could also be considered if the cost and complexity of testing were low.

WD is caused by various mutations within the ATP7B (ATPase 7B, copper transporting protein/enzyme) gene. Among the ethnic groups tested so far, some have predominant distinct mutations. The p.H1069Q mutation is detectable in up to 60% of disease-causing alleles in Central Europe (4,5), the p.R778L mutation is detectable in up to 45% in China (6), whereas the c.3402delC mutation is detectable in up to 30% in Brazil (7). Therefore, depending on the ethnic background, distinct mutations can be first screened. However, subsequent genetic analysis remains demanding because >400 mutations within ATP7B have been already recorded, and most patients are compound heterozygote.

In this issue, Gupta et al. (8) describe an “Effective molecular diagnosis of Wilson disease using prevalent mutations and informative SNP [single-nucleotide polymorphism] markers” in a multietnic WD cohort from India. They report on the most prevalent p.G1061E mutation in their cohort identified in 11% of analyzed WD chromosomes and suggest that this mutation together with 4 other already published mutations in India may be used in initial mutational screening. When none of these 5 disease-causing mutations is detected on either allele, Gupta et al. (8) suggest the analysis of 4 informative SNP markers within ATP7B, which they identified in a cohort of 1871 analyzed patients. Using this approach they provide evidence that in 25 of 28 patients derived from 17 unrelated WD families they were able to predict the WD carrier status. The additional use of well-established microsatellite markers enabled them to obtain information on the genotype in the remaining 3 patients.

The significance of this report is to describe a new approach for genetic testing in patients with WD. Intragenic SNPs for identifying WD have never been highlighted before, and they offer a breakthrough in genetic screening for WD. For many years microsatellite markers have been used, but their prediction is limited by recombinant events. The identification of these 4 SNPs as markers will mostly overcome the limitations of microsatellite markers. A multiplex PCR approach may easily cover these mutations in a single test. It will improve diagnostic testing in WD in India, but will also be applicable to other populations. Larger cohorts with different ethnic origin have to be tested to confirm these findings. The proposed approach is likely to be more feasible than sequencing of all exons for routine diagnostics, but a direct comparison of these 2 approaches must be performed.

Genetic testing of mutationally heterogeneous diseases is difficult. We are currently developing a diagnostic DNA chip to identify 60 WD mutations to approach this problem, but still we will miss rare and new mutations with our method. Thus, the inclusion of SNP markers in the genetic diagnostics for WD is highly important. Therefore, I conclude that a more general genetic diagnostic algorithm in presymptomatic and symptomatic WD may be applicable in the future, which could include the following 3 steps:

1. Testing in a single assay, using a technique such as multiplex PCR, for the predominant mutations that are expected based on the ethnic origin.
2. Intragenic SNP and microsatellite marker analysis will be done to identify WD alleles.
3. Direct sequencing after affected alleles have been identified.

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References

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