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A report of whole-genome sequencing in neurologic Wilson's disease

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Sir,

Patients with neurologic Wilson's disease (WD) often suffer from a diagnostic delay or misdiagnosis due to an atypical presentation. This may include the concomitant presence of motor signs with variable severity and psychiatric symptoms without noticeable hepatic symptoms.[1],[2] A prompt molecular testing of ATP7B (MIM: 606882) is often required in neurologic WD patients to confirm the clinical diagnosis and to facilitate screening of the family members.[3] Traditional ATP7B testing method is time-consumingand includes Sanger sequencing of the ATP7B exons followed by deletion/duplication analysis, if required. Recent advances in the whole-genome sequencing (WGS) technologies combined with the cost reduction and standardization of data processing make WGS a potentially universal time and cost effective molecular diagnostic tool. We evaluated the diagnostic utility

of the WGS in a family with autosomal recessive Parkinson's like gait disorder suggestive of neurologic Wilson's disease (WD).

A 21-year male ([Table 1]: Case ID, II:1) presented with a 6-month history of frequent bilateral and vocal tremors with walking difficulty and bilateral cogwheel rigidity. The movement disorder in this patient worsened over time with the development of dysarthia, drooling and facial dystonia. Laboratory findings indicated a near absence of ceruloplasmin in this patient. The liver function test results did not show abnormalities and no liver biopsy was performed. Pedigree analysis identified a sibling ([Table 1]: Case ID, II:2) with similar clinical symptoms. The demographic and clinical features of both patients at the initial presentation are described in [Table 1]. WGS and analysis was performed for one patient (II: 1) using TruSeq Nano DNA library preparation protocol and Illumina HiSeq X Ten sequencing as described previously.[4] We integrated the available genetic and clinical information in the WGS data analysis by considering variants that were homozygous or compound heterozygous found in the genes previously implicated in disorders exhibiting Parkinson-like gait abnormalities (gene list available upon request). Out of 23 variants complying with the above mentioned criteria, only homozygous missense variant (c.2930C>T; p.T977M, CADD [5] score 29.7) in the ATP7B co-segregated with the disease in this family. An ophthalmologic re-evaluation revealed Kayser-Fleischer rings in both patients [Figure 1]. These findings strongly supported a diagnosis of Wilson's disease with neurologic manifestations.{Table 1}{Figure 1}

Due to the presence of time-consuming traditional sequencing methods, many diagnostic facilities have switched to next-generation sequencing based approach involving enrichment of genomic regions harboring ATP7B coding sequences followed by massively parallel sequencing as the preferred method for molecular diagnosis of Wilson's disease.[6] It, however, requires designing and validating probe- or PCR-based target capture assays to enrich relevant genomic sequences. Our study exemplifies that a prompt whole-genome sequencing assay with the standard method, when combined with clinical and genetic information, identifies the disease mutation with the same efficacy as the targeted approaches. At the same time, it overrides the need for prior target enrichment, thereby reducing optimization time and cost.

The load of recessive genetic disorders is higher in the South Asian population due to the practice of consanguineous marriages. Whole genome-sequencing combined with disease centered variant identification can, therefore, provide a time and cost effective generic molecular diagnostic tool as described in our study. Furthermore, by replacing single-gene approaches in the clinical diagnostic settings, WGS has the potential to accelerate the identification of novel population-specific, clinically relevant, genetic variants for screening and management of genetic diseases in the South Asian population.

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Conflicts of interest

There are no conflicts of interest.

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