Indian Journal of Pediatrics (March 2023) 90(3):219
https://doi.org/10.1007/s12098-022-04428-1

EDITORIAL COMMENTARY

Wilson Disease—Genomic Complexities Yet to Be Unveiled!

Mounika Endrakanti[1] · Madhulika Kabra[1] · Neerja Gupta[1]

Received: 23 November 2022 / Accepted: 1 December 2022 / Published online: 6 January 2023

Wilson disease (WD), a disorder of impaired copper metabolism caused by pathogenic variants in *ATP7B*, is characterized by hepatic and neuropsychiatric symptoms and accounts for 7.6% of hepatobiliary diseases in South India [1].

Approximately 900 *ATP7B* mutations have been described, with missense and frameshift mutations being the most common, followed by nonsense mutations affecting the copper transporter's stability or residual activity, respectively [2]. Several geographically prevalent variants have been described, including c.3207C>A (p.H1069Q) from Europe and c.2333G>T (p.R778L) from Asia [2, 3]. The most common variant in India is c.813C>A (p.C271*) [1]. In this issue of the Journal, Nagral et al. [4] have reported this variant in 24% ($N = 18/75$) mutant alleles from 58 unrelated patients from various parts of India, with an overall diagnostic yield of 64% ($N = 37/58$) using multimodality genetic testing. The Sanger sequencing identified 33 pathogenic/likely pathogenic variants (29 exonic and four intronic variants), including six novel variants. In this study, MLPA and whole-exome sequencing were not diagnostic. Among various WD cohorts from India and other countries, a highly variable diagnostic yield ranging from 56% to 98% has been reported [4–6]. Possible explanations include differences in the testing strategies, epigenetic mechanisms, or inherent limitations of the testing methodology in detecting deep intronic variants. This study [4], like most large WD cohorts described to date, was unable to detect genotype–phenotype correlations [7]. Earlier reports described an early-onset severe disease in Indian patients with the common truncating mutation c.813C>A (p.C271*), and a late-onset predominantly neurological phenotype in patients with the common European variant, c.3207C>A (p.H1069Q) [2]. The genotype–phenotype matrix proposed by Mukherjee et al. could be useful in identifying patients with a potential for divergent phenotypes based on genotype [6].

Intrafamilial variability, significant genetic heterogeneity, variable age of onset, hepatic and/or neuropsychiatric manifestations, and response to treatment, all point to the presence of additional modifying factors such as *ATP7B* polymorphisms and modifier genes. It may also be influenced by the complex interplay of epigenetic mechanisms in the regulation of gene expression and dysregulated methionine metabolism, as previously described in WD animal models [2, 8]. To sum up, the combined effect of epigenetic factors and genetic variations in humans to explain the complex phenotypes of WD needs to be investigated further.

Declarations

Conflict of Interest None.

References

1. Bhattacharya K, Thankappan B. Wilson's disease update: An Indian perspective. Ann Indian Acad Neurol. 2022;25:43–53.
2. Medici V, LaSalle JM. Genetics and epigenetic factors of Wilson disease. Ann Transl Med. 2019;7:S58.
3. Chang IJ, Hahn SH. The genetics of Wilson disease. Handb Clin Neurol. 2017;142:19–34.
4. Nagral A, Mallakmir S, Garg N, et al. Genomic variations in ATP7B gene in Indian patients with Wilson disease. Indian J Pediatr. 2022. https://doi.org/10.1007/s12098-022-04250-9.
5. Aggarwal A, Chandhok G, Todorov T, et al. Wilson disease mutation pattern with genotype-phenotype correlations from western India: confirmation of p.C271* as a common indian mutation and identification of 14 novel mutations. Ann Hum Genet. 2013;77:299–307.
6. Mukherjee S, Dutta S, Majumdar S, et al. Genetic defects in Indian Wilson disease patients and genotype-phenotype correlation. Parkinsonism Relat Disord. 2014;20:75–81.
7. Ferenci P, Stremmel W, Członkowska A, et al. Age and sex but not ATP7B genotype effectively influence the clinical phenotype of Wilson disease. Hepatology. 2019;69:1464–76.
8. Mordaunt CE, Shibata NM, Kieffer DA, et al. Epigenetic changes of the thioredoxin system in the tx-j mouse model and in patients with Wilson disease. Hum Mol Genet. 2018;27:3854–69.

✉ Neerja Gupta
neerja17aiims@gmail.com

[1] Division of Genetics, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India