Liver Research xxx (2017) 1–10

Contents lists available at ScienceDirect

Liver Research

journal homepage: http://www.keaipublishing.com/en/journals/liver-research

Review Article

Wilson disease: At the crossroads between genetics and epigenetics—A review of the evidence

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ARTICLE INFO

Article history:
Received 6 December 2016
Received in revised form
23 February 2017
Accepted 27 February 2017

Keywords:
Wilson disease
Modifier gene
Epigenetics
Mitochondria

ABSTRACT

Environmental factors, including diet, exercise, stress, and toxins, profoundly impact disease phenotypes. This review examines how Wilson disease (WD), an autosomal recessive genetic disorder, is influenced by genetic and environmental inputs. WD is caused by mutations in the copper-transporter gene *ATP7B*, leading to the accumulation of copper in the liver and brain, resulting in hepatic, neurological, and psychiatric symptoms. These symptoms range in severity and can first appear anytime between early childhood and old age. Over 300 disease-causing mutations in *ATP7B* have been identified, but attempts to link genotype to the phenotypic presentation have yielded little insight, prompting investigators to identify alternative mechanisms, such as epigenetics, to explain the highly varied clinical presentation. Further, WD is accompanied by structural and functional abnormalities in mitochondria, potentially altering the production of metabolites that are required for epigenetic regulation of gene expression. Notably, environmental exposure affects the regulation of gene expression and mitochondrial function. We present the "multi-hit" hypothesis of WD progression, which posits that the initial hit is an environmental factor that affects fetal gene expression and epigenetic mechanisms and subsequent "hits" are environmental exposures that occur in the offspring after birth. These environmental hits and subsequent changes in epigenetic regulation may impact copper accumulation and ultimately WD phenotype. Lifestyle changes, including diet, increased physical activity, stress reduction, and toxin avoidance, might influence the presentation and course of WD, and therefore may serve as potential adjunctive or replacement therapies.

1. Introduction

There is mounting evidence that the phenotypic expression of genetic diseases is governed by modifiable environmental inputs, including diet,[1] exercise,[2,3] stress,[4] and toxins.[5] These factors impact disease phenotypes through several mechanisms, including alterations in mitochondrial function and epigenetic regulation of gene expression. The ability to modify the phenotype of a genetic disease through lifestyle changes is valuable, because there are often limited treatment options for such conditions. This review will discuss the evidence that the phenotype of Wilson disease (WD) is influenced by interacting genetic and epigenetic factors, affecting the regulation of gene expression and potentially WD onset and progression.

2. Clinical presentation and treatment of Wilson disease

WD is an autosomal recessive disorder that is caused by mutations in *ATP7B*, which encodes for a P-type ATPase that is primarily expressed in the brain and liver.[6] In the liver, ATP7B traffics excess copper to the hepatocyte plasma membrane for excretion into bile and loads copper onto the ferroxidase protein ceruloplasmin.[6] WD is characterized by the accumulation of copper in the liver and brain, effecting hepatic, neurological, and psychiatric symptoms. The severity of these symptoms varies widely. Liver manifestations range from mild elevation of liver enzymes to acute liver failure and cirrhosis.[7,8] The neurological effects can be similar to those of Parkinson disease and include tremors, dysarthria, and ataxia.[9] The psychiatric symptoms include anxiety, depression, disinhibition, and personality changes.[10]

Edited by Peiling Zhu and Genshu Wang.

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https://doi.org/10.1016/j.livres.2017.08.003

Please cite this article in press as: Kieffer DA, Medici V, Wilson disease: At the crossroads between genetics and epigenetics—A review of the evidence, Liver Research (2017), https://doi.org/10.1016/j.livres.2017.08.003

The age of onset of WD also widely varies. Liver manifestations that are related to WD have been reported to first appear in patients aged as young as 9 months and in those aged over 70 years.[11,12] Although the course of the disease tends to be benign if it is diagnosed early, the response to copper chelation or zinc treatment varies and can be accompanied by many side effects.[13,14]

Two therapies commonly prescribed for WD are zinc salts and copper chelators. These can be used alone or in combination. Zinc inhibits intestinal absorption of dietary copper,[15] and copper chelators bind copper in the blood and tissues for subsequent excretion in the urine. Zinc monotherapy is less effective than copper chelators in the treatment of hepatic WD.[13] In a small study, zinc treatment improved the neurological symptoms in patients with WD.[14] A retrospective study that compared the effects of two copper chelation therapies in 405 patients with WD found more patients discontinued D-penicillamine compared with trientine due to adverse reactions.[16] Also, regardless of copper chelator, hepatic improvements were observed in more than 90% of patients, whereas 55% of patients experienced neurological improvements. In 7% of patients, neurological symptoms worsened after copper chelation therapy was initiated,[16] which is believed to be attributed to over-mobilization of free copper.[17]

Another study utilizing brain magnetic resonance imaging (MRI) also found variable responses to D-penicillamine when combined with zinc sulfate in 50 patients with the neurological manifestation of WD.[18] Based on the MRI scans, 35 patients improved, 9 remained stable, 4 declined, and 1 patient showed signs of improvement and decline. These data support the need for adjunctive or alternative therapies for patients who fail to respond adequately or experience adverse reactions to traditional treatments.

3. Genetics of Wilson disease

Recent genetic studies reported a prevalence of 1:7026 for two mutant pathogenic *ATP7B* alleles,[19] indicating that WD is more frequent than initially described (1:30,000).[20,21] Over 500 mutations in *ATP7B* have been identified, 380 of which have been deemed to be disease-causing mutations.[22] Most of these changes are missense mutations, small insertions and deletions in the coding region, or splice junction mutations. Whole-exon deletions, mutations in the promoter region, and multiple mutations within the same gene also occur but are less common (for a recent review).[23] These various mutations decrease ATP7B levels, cause improper protein localization, reduce substrate binding (copper, ATP) or activity.[24–26]

Attempts to link specific gene mutations to phenotypic outcomes have provided little explanation for the highly varied presentation of WD.[27–30] Studies have found a correlation between p. H1069Q mutations, which are the most common mutations in European populations, and late onset of WD[31,32]—an association that Merle et al. challenged.[33] A correlation between truncated *ATP7B* mutations and early-onset WD has also been observed in Europeans,[33–35] but other studies have not been able to corroborate these findings.[36–38] The overall lack of a clear genotype-phenotype relationship has spurred researchers to investigate other mechanisms—including modifier genes and epigenetic regulation of gene expression—to account for the pleiotropic effects of WD.

4. Potential modifier genes

Modifier genes affect the expression of other genes,[39] impacting disease-related phenotype, for instance, by altering expressivity—the degree to which a particular trait is expressed. *ATP7B* modifier genes are believed to influence tolerance to copper accumulation and copper storage capacity.[40] Several modifier genes of *ATP7B* have been analyzed and are described briefly below. The results from these studies are often conflicting, likely due to their small cohorts and the heterogeneity of *ATP7B* mutations, necessitating further examination to explain the highly varied phenotypic presentation of WD.

4.1. Copper metabolism domain-containing 1 (COMMD1)

COMMD1 is a copper chaperone that interacts directly with the N-terminus of ATP7B.[41] Mutations in *COMMD1* cause canine copper toxicosis in Bedlington terriers.[42] No exonic mutations in *COMMD1* have been identified in patients with WD.[43] An association between a *COMMD1* polymorphism [Asn 164 (GAT/GAC)] and early onset of neurological and hepatic symptoms was reported in WD patients who were homozygous for the most common *ATP7B* mutation, H1069Q.[43] But, subsequent studies have not been able to confirm this finding.[44,45]

4.2. Antioxidant 1 copper chaperone (ATOX1)

ATOX1, similar to COMMD1, is a copper chaperone that associates directly to ATP7B. By modulating the amount of copper that binds to ATP7B, ATOX1 influences the intracellular localization,[46] posttranslational modification, and enzymatic activity of ATP7B.[47] ATOX1 is also a copper-dependent transcription factor that is involved in cell proliferation.[48] Despite the physical interaction between ATOX1 and ATP7B, a study in patients with WD failed to identify any significant non-synonymous coding variations in *ATOX1* beyond the expected frequencies.[44,49]

4.3. X-linked inhibitor of apoptosis (XIAP)

XIAP is an anti-apoptotic protein and a potential regulator of copper-induced cell injury. The binding of copper to XIAP relieves the inhibition of caspase, thereby initiating caspase-mediated cell death in copper-loaded hepatocytes.[50] XIAP might also maintain cellular copper homeostasis by promoting ubiquitination and degradation of COMMD1.[51] In support of this model, experiments in Xiap-deficient mice yielded lower cellular copper levels and modestly increased levels of COMMD1.[51] Four non-synonymous coding SNPs have been described in the coding region of *XIAP*,[52,53] but their function remains unknown. In 98 WD patients,[54] the frequency of 7 SNPs identified in the *XIAP* gene did not differ significantly from previous reports, and the statistical analysis did not reveal any correlation between each *XIAP* SNP and age of onset or clinical presentation (hepatic vs. neurological vs. mixed vs. asymptomatic).[54]

4.4. Patatin-like phospholipase domain-containing 3 (PNPLA3)

PNPLA3 is a lipase that targets triglycerides.[55] Several studies have shown that a missense mutation (I148M) in *PNPLA3* increases hepatic fat deposition.[56] Hepatic fat accumulation is a hallmark of WD; therefore, the prevalence of *PNPLA3* mutations was investigated in 98 patients with WD.[22] Multivariate logistic regression revealed the *PNPLA3* G allele was an independent variable associated with moderate/severe steatosis, whereas hepatic copper content was not.[22]

4.5. Apolipoprotein E (APOE)

APOE has a significant role in lipid transport. There are 3 isoforms of APOE: ε2, ε3, and ε4.[57] The presence of the *APOE*ε4 allele is associated with an increased risk of developing Alzheimer disease,

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