Influence of Homozygosity for Methionine at Codon 129 of the Human Prion Gene on the Onset of Neurological and Hepatic Symptoms in Wilson Disease

Uta Merle, MD; Wolfgang Stremmel, MD; Reinhard Geßner, PhD

**Background:** The clinical heterogeneity of Wilson disease expression cannot be fully explained by the various mutations of the Wilson disease gene. The prion-related protein (PrP) has been shown to bind copper in vitro and might therefore influence Wilson disease.

**Objective:** To examine the effect of the PrP polymorphism at codon 129, resulting in either methionine or valine (M129V), on the clinical phenotype of patients with Wilson disease.

**Design and Setting:** Retrospective cross-sectional study at a university hospital.

**Participants:** A total of 134 patients were grouped according to their PrP M129V genotypes and initial clinical symptoms (hepatic vs neurological).

**Results:** The onset of symptoms was significantly delayed in patients homozygous for the 129M allele as compared with patients with at least 1 V allele (mean ± SD age, 20.90 ± 11.9 years vs 15.5 ± 7.6 years; *P* = .003). No significant correlation was found when analyzing the impact of the PrP M129V genotype on the clinical symptoms at initial manifestation (hepatic vs neurological; *P* = .44).

**Conclusion:** This study shows for the first time, to our knowledge, that the human PrP polymorphism M129V influences the onset of symptoms in patients with the copper storage disorder Wilson disease.

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ference in genotype frequency between patients with WD and healthy subjects of central European descent, (2) the impact of PrP M129V genotypes on phenotypic disease expression (hepatic vs neurological), and (3) the influence of the PrP M129V genotype on the onset of initial symptoms in patients with WD.

**RESULTS**

A total of 134 patients with symptomatic WD (78 women, 56 men) were analyzed for a potential correlation between the PrP M129V genotype, the phenotypical disease expression, and age at onset of symptoms. Of those, 46 patients (34%) were initially seen with neurological symptoms and 88 patients (66%), with hepatic symptoms. Patients with neurological symptoms were older at initial manifestation than patients with hepatic dysfunction (mean±SD age, 19.1±8.3 years vs 15.2±7.6 years, P = .009). The Table shows the breakdown of distribution of the PrP M129V genotype, ApoE genotype, and the ATP7B H1069Q mutation status. No sex-specific differences were found with respect to clinical symptoms (neurological vs hepatic) and the PrP 129 geno-
The overall PrP M129V genotype distribution in our patients was similar to that of a cross-sectional control sample (Table) and values published for healthy European subjects. There was also no significant difference between the 2 subgroups classified according to the clinical symptoms at initial manifestation (P = .44) (Table).

Age at onset of symptoms was investigated in patients with WD, comparing prion-related protein (PrP) at codon 129 resulting in homozygous methionine (129M/M) and PrP at codon 129 resulting in either methionine or valine (129V+). Data are expressed as mean±SD. A, All patients with WD and subgroups defined by their ATP7B H1069Q and apolipoprotein E (ApoE) genotype. B, Patients with WD divided in 2 subgroups defined by initial clinical manifestation, hepatic (n = 88) or neurological (n = 46).

Our data show no difference in PrP M129V genotype frequency between a cohort of 134 patients with WD and healthy European subjects, indicating that this polymorphism has no influence on the penetrance of WD. No significant correlation was found when analyzing the influence of the PrP M129V genotype on clinical symptoms at initial examination (hepatic vs neurological; P = .44). However, whether the PrP M129V genotype has an influence on severity of symptoms and on long-term outcome during therapy has to be analyzed in future studies.

In our study, the PrP 129M/M genotype was established as an important factor in delaying the onset of neurological and hepatic symptoms. This observation is novel and highly relevant, as there are currently no known genetic and/or environmental disease modifiers of this clinically highly variable disorder. While our study was not designed to test biochemical mechanisms that may explain the later onset of neurological and hepatic symptoms associated with the PrP 129M/M genotype in patients with WD, other investigators demonstrated copper ion binding and antioxidative properties of PrP in vitro. It is conceivable that PrP may have an important role in cellular copper metabolism, which may be affected by the PrP M129V polymorphism. The identification of the PrP M129V polymorphism modulating onset of the copper storage disorder WD could potentially help to elucidate the role of PrP in copper metabolism and in WD manifestation.
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Correspondence: Uta Merle, MD, Department of Gastroenterology and Hepatology, University Hospital, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany (uta_merle@med.uni-heidelberg.de).

Author Contributions: Prof Dr Stremmel and Dr Geßner contributed equally to this work. Dr Merle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Merle, Stremmel, and Geßner. Acquisition of data: Merle and Geßner. Analysis and interpretation of data: Merle and Geßner. Drafting of the manuscript: Merle. Critical revision of the manuscript for important intellectual content: Merle, Stremmel, and Geßner. Statistical analysis: Merle and Geßner. Administrative, technical, and material support: Merle and Stremmel. Study supervision: Merle, Stremmel, and Geßner.

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REFERENCES


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