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Genetic aspects of human prion diseases

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Human prion diseases are rapidly progressive and fatal neurodegenerative conditions caused by a disease-causing isoform of the native prion protein. The prion protein gene (*PRNP*) encodes for the cellular prion protein, which is the biological substrate for prion disease transmission and neurotoxicity. Human prion diseases have three etiologies: sporadic, genetic, and acquired. *PRNP* polymorphisms and pathogenic variants play a large role in the frequency, age at onset, and clinicopathologic phenotype of prion diseases. Genetic prion diseases will be covered in detail and information necessary for clinical care, predictive genetic testing, and genetic counseling will be reviewed. Because the prion protein is necessary for transmission and neurotoxicity, many experimental treatments targeting its production are being investigated and hold potential promise as a disease modifying treatment for all forms of prion disease, including asymptomatic mutation carriers. This article will review genetic aspects of human prion disease and their influence on epidemiology, clinicopathologic phenotype, diagnostics, clinical management, and potential treatment approaches.

KEYWORDS

prion disease, Creutzfeldt-Jakob disease, Gerstmann-Sträussler Scheinker disease, fatal familial insomnia, genetic Creutzfeldt-Jakob disease, genetics, prion protein, *PRNP*

Introduction

Prion diseases are rapidly progressive neurodegenerative conditions that are invariably fatal. Disease causing prions (PrP^D) cause neurotoxicity and employ template directed protein misfolding to convert normal cellular prion protein (PrP^C) into more PrP^D . PrP^C is necessary for neurotoxicity and for disease propagation (1). Prion protein gene (*PRNP*) knock-out mice are resistant to developing scrapie when they are intracerebrally inoculated (2). Similarly, *PRNP* knockout mice are unable to propagate the disease, demonstrating that PrP^C is necessary for the clinical manifestation of disease and its transmission (3). Prion diseases affect a variety of animal species such as scrapie in sheep and goat, bovine spongiform encephalopathy in cattle, and chronic wasting disease in cervids.

Genetic Aspects Of Human Behavior

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