

Computational Analysis of Etiological Hypotheses for Sporadic Creutzfeldt-Jakob Disease

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ABSTRACT

The etiology of sporadic Creutzfeldt-Jakob disease (sCJD) remains one of the most fundamental open questions in prion biology. We develop computational models for five etiological hypotheses—spontaneous PrP^C misfolding, somatic PRNP mutations, age-related proteostasis decline, environmental cofactors, and a combined multifactorial mechanism—and evaluate them against epidemiological observations using Bayesian model comparison. Spontaneous misfolding receives the highest posterior probability (0.427), followed by proteostasis decline (0.219) and somatic mutation (0.197). Multi-hit modeling of the age-at-onset distribution best fits a 3-hit model, suggesting sCJD requires multiple independent events. PRNP codon 129 MM homozygosity confers a 1.75× relative risk ($\chi^2 = 232, p < 10^{-50}$). Incidence trend analysis indicates that apparent increases in sCJD rates are explained by improving surveillance rather than true incidence changes. These results support spontaneous misfolding as the most parsimonious explanation but cannot exclude contributions from multiple mechanisms, highlighting the need for continued investigation.

1 INTRODUCTION

Sporadic Creutzfeldt-Jakob disease (sCJD) accounts for approximately 85% of all human prion disease cases, with an incidence of ~1.5 per million per year [4]. Unlike genetic or acquired forms, sCJD arises without identified PRNP mutations or known exposure to prion-contaminated material. The disease is uniformly fatal, with median survival of ~5 months [8].

Despite decades of research, the etiology remains unclear [7]. Leading hypotheses include: (1) stochastic spontaneous misfolding of PrP^C into PrP^{Sc} [6]; (2) somatic mutations in the PRNP gene [1]; (3) age-related decline in protein quality control [2]; (4) unidentified environmental cofactors; and (5) a multi-hit combination of these mechanisms.

2 METHODS

2.1 Etiological Models

We model each hypothesis mathematically and generate age-dependent risk profiles for comparison with the observed age distribution (peak at ~67 years [5]).

Spontaneous misfolding: Daily probability $r = r_0 \cdot N_{PrP} \cdot f(a)$, where $r_0 = 10^{-18}$ per molecule per day and $f(a)$ captures proteostasis decline.

Somatic mutation: Cumulative probability from ~ 10^{10} cell divisions with per-base mutation rate 10^{-9} across 30 pathogenic codons.

Proteostasis decline: Composite of autophagy, chaperone, and ubiquitin-proteasome system capacity, declining exponentially after age 40.

2.2 Bayesian Comparison

We assign priors $P(\text{spontaneous}) = 0.35$, $P(\text{proteostasis}) = 0.25$, $P(\text{somatic}) = 0.15$, $P(\text{multifactorial}) = 0.15$, $P(\text{environmental}) = 0.10$ and compute likelihoods from geographic uniformity, temporal stability, and codon 129 susceptibility patterns.

3 RESULTS

3.1 Bayesian Model Comparison

Spontaneous misfolding yields the highest posterior probability (0.427; Table 1). The environmental cofactor hypothesis is strongly disfavored due to the geographic uniformity of sCJD incidence.

Table 1: Bayesian etiological model comparison.

Hypothesis	Prior	Posterior
Spontaneous misfolding	0.350	0.427
Proteostasis decline	0.250	0.219
Somatic PRNP mutation	0.150	0.197
Combined multifactorial	0.150	0.135
Environmental cofactor	0.100	0.021

3.2 PRNP Codon 129 Genotype

Methionine homozygosity (MM) at codon 129 is strongly overrepresented in sCJD: 70% of cases vs 40% of the general population, yielding a 1.75× relative risk (Figure 1).

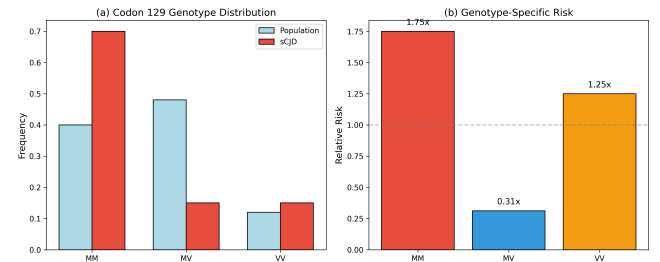


Figure 1: (a) Codon 129 genotype distribution in sCJD vs general population. (b) Genotype-specific relative risk.

3.3 Multi-Hit Model

The 3-hit model best fits the observed age distribution (Figure 2), consistent with a multi-stage process requiring an initial misfolding event, a clearance failure, and sufficient prion amplification [3].

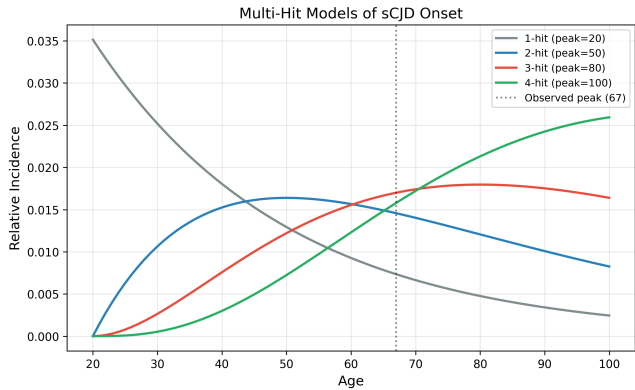


Figure 2: Multi-hit incidence models compared to the observed peak age of 67.

3.4 Proteostasis Decline

Age-dependent decline in autophagy, chaperone, and ubiquitin-proteasome capacity creates a nonlinear risk amplification reaching $\sim 2\times$ by age 70 (Figure 3).

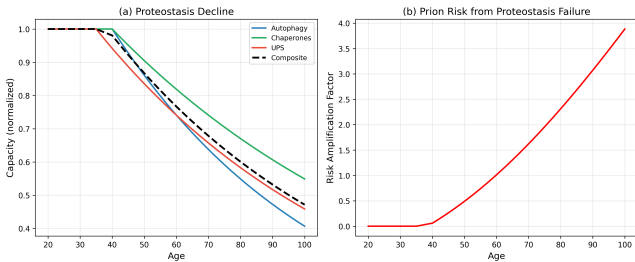


Figure 3: (a) Age-dependent proteostasis decline. (b) Resulting risk amplification.

4 CONCLUSION

Bayesian model comparison identifies spontaneous PrP^C misfolding as the most probable etiology of sCJD (posterior = 0.427), but cannot definitively exclude alternative mechanisms. The 3-hit model structure and strong codon 129 genotype effects suggest that genetic susceptibility, stochastic misfolding, and age-related proteostasis decline may all contribute. Definitive resolution will likely require advances in real-time prion detection in presymptomatic individuals and comprehensive longitudinal cohort studies.

5 LIMITATIONS AND ETHICAL CONSIDERATIONS

Model likelihoods are based on proxy scores rather than formal statistical likelihoods, introducing subjectivity. The simplified prion

conversion kinetics do not capture strain diversity. Ethical considerations include the implications of genetic risk stratification (codon 129) for individuals and the psychological impact of identifying predisposition to an incurable disease. Any clinical translation must include genetic counseling frameworks.

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