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TOPIC:

Genetic Adaptation and Disease Resistance: Investigating the Association Between Kuru and Human Evolutionary Response

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1. Abstract

This proposal investigates the genetic response of the Fore people of Papua New Guinea to the kuru epidemic, one of the clearest documented cases of rapid natural selection in living human populations. Kuru is a fatal prion disease transmitted through endocannibalistic mortuary practices, caused by misfolded prion protein (PrPSc) that destroys brain tissue. The epidemic imposed intense selective pressure on the prion protein gene (PRNP), enriching two protective variants: heterozygosity at codon 129 (M129V) and a novel variant at codon 127 (G127V). This study combines Systematic Literature Synthesis, Comparative Allele-Frequency Mapping and Hardy-Weinberg Deviation Analysis to clarify how these variants spread, assess global evidence of balancing selection at PRNP, and evaluate G127V as a therapeutic lead for contemporary prion diseases such as Creutzfeldt-Jakob disease (CJD).

2. Introduction

Kuru was first documented in 1957 by Gajdusek and Zigas among Fore communities in the Eastern Highlands of Papua New Guinea. The disease spread through consumption of brain tissue at mortuary feasts, disproportionately affecting women and children who preferentially ate neural tissue. At peak incidence, kuru mortality was high enough to create measurable gender imbalances within villages. Following the suppression of endocannibalism by the late 1950s, case numbers declined steadily; the last confirmed case was recorded in 2005. Research by Mead et al. (2003) showed that elderly survivors were significantly enriched for PRNP codon 129 heterozygosity compared to younger unexposed Fore, indicating that the epidemic had driven strong balancing selection at this locus. A subsequent 2009 study identified G127V, a novel variant found exclusively in individuals from the epidemic epicenter, absent in all kuru patients and in all unexposed populations worldwide (Mead et al., 2009). Asante et al. (2015) later confirmed through transgenic mouse models that G127V confers complete resistance to kuru and classical CJD prions, positioning it as both a remarkable evolutionary event and a promising therapeutic target.

3. Literature Review

The Fore epidemic was culturally embedded in mortuary practices documented by Lindenbaum (1979), whose anthropological work explained how gender-based patterns of consumption drove the sex differential in mortality. Mead et al. (2003) provided the foundational genetic evidence of balancing selection, demonstrating that worldwide PRNP haplotype diversity is inconsistent with neutral evolution and suggesting that kuru-like prion epidemics may have recurred throughout human prehistory. The codon 129 M129V polymorphism is globally distributed and modulates susceptibility to multiple prion diseases, while G127V is geographically restricted to the Purosa Valley epicenter, indicating it arose from a single common ancestor just before the epidemic began (Mead et al., 2009). Molecular dynamics simulations suggest G127V disrupts the beta-2/alpha-2 loop region of PrP, inhibiting dimer and fibril formation central to prion propagation. A 2025 preprint further demonstrated that inducible G127V expression suppresses prion infection across a broad range of prion strains in cell lines, strengthening its therapeutic relevance. Together, these findings establish kuru as both a historical tragedy and a uniquely informative model of disease-driven human evolution.

PRNP Codon 129 and Survivor Genetics

Collinge (2001) established that heterozygosity at PRNP codon 129 is a protective factor across multiple prion disease types, because the structural mismatch between methionine- and valine-encoding variants slows the molecular templating on which prion propagation depends. Building on this, Mead et al. (2003) demonstrated that elderly Fore women who had attended numerous funeral feasts without contracting kuru showed a statistically significant excess of methionine-valine heterozygotes relative to unexposed younger Fore, and that the Fore population as a whole carried a valine-129 allele frequency of 0.55, the highest ever recorded globally. Mead et al. (2008) later placed these findings in a broader

evolutionary context, noting that similar valine frequency elevations appear in other populations with histories of cannibalistic burial practices, suggesting that prion-driven selection at this locus may have recurred across human prehistory.

4. Methodology

(1) Systematic Literature Synthesis with Quality Appraisal. A formal systematic review was conducted following the PRISMA 2020 guidelines. Database searches were carried out in PubMed/MEDLINE, Web of Science, Scopus, and EMBASE, with supplementary citation-chain searching in Google Scholar. Three thematic areas guided the search: the clinical and epidemiological profile of kuru; PRNP genetics and prion disease susceptibility; and disease-driven genetic adaptation in human populations. For each area, Boolean search strings were built using MeSH controlled vocabulary combined with free-text keywords. No lower date limit was set for publication year, and coverage extended to April 2025. Articles were included if they reported original empirical findings or systematic analytical work relevant to at least one of the three areas, were published in peer-reviewed English-language sources, and used verifiable methods. Two reviewers independently screened titles and abstracts before proceeding to full-text review, resolving any disagreements through discussion. Quality of included studies was assessed with the Newcastle-Ottawa Scale for observational and cohort designs, and overall strength of evidence was rated under the GRADE framework.

(2) Comparative Allele-Frequency Mapping and Hardy-Weinberg Deviation Analysis. Genotype count and allele frequency data for PRNP codons 127 and 129 were taken from published primary studies and sorted into a stratification matrix covering four variables: kuru exposure zone (high for index values above 200; intermediate for 30 to 200; low for below 30; and unexposed for those with no documented funeral feast attendance as classified by Mead et al.); biological sex; age cohort at sampling; and linguistic group. Chi-square tests of Hardy-Weinberg equilibrium were applied to each stratum, and a Mantel-Haenszel pooled test was run across strata to control for confounding from population structure. Spearman rank correlations were calculated between village-level exposure index scores and local frequencies of the V129 and V127 alleles to test for geographic gradients consistent with a selection gradient. Published PRNP codon 129 genotype frequencies from diverse global populations were compiled to place the Fore data in a worldwide comparative context. Linkage disequilibrium between the G127V and M129V variants was estimated from published haplotype tables using D-prime and r-squared.

5. References

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