A novel PRNP-G131R variant associated with familial prion disease

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Roughly 40 autosomal dominant mutations of the prion protein gene (*PRNP*) cosegregate with familial Creutzfeldt-Jakob disease (CJD), fatal familial insomnia, or Gerstmann-Sträussler-Scheinker disease (GSS). Genetic prion disease in African Americans is rarely reported. We sequenced the *PRNP* coding segment of a 43-year-old African American woman with rapidly progressive dementia and a positive family history of early onset dementia not previously recognized as genetic prion disease.

**Case report**

A 43-year-old woman previously unknown to the University of Chicago was transferred for evaluation of possible stroke causing a fall and altered mental status. Nine months earlier, she developed mild dizziness/vertigo/disequilibrium that was managed with meclizine. Three months before admission, the patient stopped working because of cognitive problems; the family reported that she had been repeating herself, misplacing items, and having word-finding difficulties for a year. She was referred for a cognitive assessment but never followed up. Her family history was remarkable for a mother and sister with a 4–5-year course of dementia and progressive gait dysfunction beginning in their 30s and 40s (figure, A).

On examination, she was alert with intermittent eye contact and oriented only to self. She was unable to name her daughter and believed she was in a school. Speech was nonfluent, agrammatical, with minimal content, and interrupted by frequent bouts of inappropriate laughter. She was bradyphrenic and only able to follow simple commands intermittently. Cranial nerves were generally intact, although assessment of ocular dysmetria and nystagmus was limited by poor attention. Strength was grossly intact, and tendon reflexes were 3+ in the upper limbs, 2+ in the lower limbs, and there was bilateral nonsustained ankle clonus with flexor plantar responses. Gait was wide-based with a short stride and moderate truncal ataxia that required one-person assist.

Serum laboratory testing was extensive and unremarkable, including complete blood count, comprehensive metabolic panel, thyroid stimulating hormone, vitamins B1, B12, E, and A, folate, ammonia, HIV, reactive plasma reagin, anti-nuclear antibody, anti-SSA antibody, anti-SSB antibody, anti-RNP antibody, anti-Smith antibody, angiotensin converting enzyme, antithyroglobulin and anti-thyroperoxidase antibodies, and a complete paraneoplastic panel, including anti-NMDA and anti-GAD65 antibodies. CSF analysis was negative for infectious or inflammatory process (white blood cell count 0, red blood cell count 16, protein 25, glucose 62, negative viral and bacterial encephalitis panel, negative oligoclonal bands, and angiotensin converting enzyme). A second lumbar puncture was performed to test for CJD biomarkers, although 14-3-3 and real time quaking induced conversion assays were reported as “inconclusive” because of blood contamination from a difficult lumbar puncture. However, T-Tau was significantly elevated at 3,026 pg/ML (values > 1,150 pg/ML support prion disease).

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EEG was slow (6–7 Hz) and without periodic sharp wave complexes. MRI diffusion-weighted imaging (DWI) revealed restricted diffusion within the bilateral basal ganglia and in a “cortical ribboning” pattern throughout multiple cortical regions, consistent with CJD (figure, B). An fluorodeoxyglucose positron emission tomography scan displayed generalized cortical and bilateral basal ganglia hypometabolism (figure, B). A full body CT with contrast was negative for tumor.

She was eventually discharged to hospice and died within 16 months of symptom onset. The family declined an autopsy.

PRNP sequencing revealed a novel single nucleotide change (c.391G>A), resulting in an arginine (R) substitution of glycine (G) at residue 131 paired with valine (V) coding at the polymorphic codon 129 (129V). The normal allele carried a single octapeptide repeat deletion, a known polymorphism, with methionine (M) at codon 129 (figure, C).

Discussion

Although found in a single patient, the early onset of disease in the proband and family members strongly supports the PRNP-G131R/129V variant as the cause of prion disease in this African American family. Assessment of this variant using the PolyPhen-2 molecular modeling software also supports a pathogenic effect (probability of 0.89–1.0). Of interest, a valine (V) substitution at
this same position, although allelic with methionine at residue 129 (PRNP-G131V/129M), was previously described in 2 families that displayed dementia preceding ataxia over a 5–15-year course. The brain histopathologic findings in those cases displayed prion protein (PrP) amyloid plaque deposition that classifies the PRNP-G131V/129M variant as GSS. Although our case lacks histopathologic classification, the rapid course and pronounced restricted diffusion on MRI, a feature that generally correlates with the underlying spongiform degeneration, support CJD as the disease subtype. However, the clinical phenotype of GSS can be quite variable and although DWI imaging is typically negative in GSS, rare cases report a positive MRI. DWI imaging associated with the PRNP-G131V/129M variant was not reported, leaving that question open. Thus, the question of whether the PRNP-G131R/129V variant predisposes PrP to misfold into a CJD-determining conformation rather than the GSS conformation induced by PRNP-G131V/129M will remain unanswered until the availability of direct histologic evidence.

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### Appendix Authors

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| Kefeng Qin, PhD | Department of Neurology, University of Chicago | Genetic sequence analysis and cloning and drafting and revising the manuscript |
| Lili Zhao, MS | Department of Neurology, University of Chicago | DNA extraction, genetic sequencing, and cloning |
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