The case report is of interest but a number of issues need to be addressed before it is acceptable for publication.

Major compulsory revisions:

1) As the authors acknowledge, the clinical profile is in keeping with sporadic Creutzfeldt-Jakob Disease (sCJD), with the routine neuropathology (spongiosis) and immunohistochemistry, showing strongly positive staining using the 3F4 antibody (when not using a prior PK digestion step), also in keeping with this diagnosis. Hence, I think the authors should consistently present the case as sCJD rather than using alternative descriptors such as “prion protein disease” or “protease-sensitive prion protein transmissible spongiform encephalopathy”. The authors can then describe how the molecular subtype and neuropathological findings do not neatly conform to one of the principal subtypes described by Parchi et al., with the abnormal prion protein isomers showing enhanced protease sensitivity (and most likely an altered conformation to that usually reported in sCJD), reminiscent of the cases reported by Gambetti et al. as “A novel human disease with abnormal prion protein sensitive to protease”. I think the authors need to be vigilant not to mislead the reader into assuming their case simply equates or approximates “protease-sensitive prionopathy” cases as reported by Gambetti et al, as there are many differences reported by the authors, viz: older age; shorter disease duration; larger vacuoloes; microglial activation; ability to detect abnormal PrP in the cerebral cortex using the 3F4 antibody on western blot; etc. Perhaps a title along the lines of: “Sporadic CJD with novel molecular subtype and increased protease sensitivity of disease-associated prion protein”.

2) The demonstrated correlation between the biochemical and immunohistochemical methods of assessing the protease sensitivity of abnormal PrP in the case is of interest. The authors need to at least immunohistochemically assess their MM1 and VV2 cases pre- and post-PK to show whether the varying levels of PK resistance demonstrated with their biochemical technique are also observed with immunohistochemistry. In addition, the authors should use a second antibody shown to be of superior utility in detecting altered conformations associated with enhanced protease sensitive PrP conformers, such as 1E4, in their immunohistochemistry pre- and post-PK, to ensure the correlation with the IDEXX technique persists. This will reassure
that the biochemical protease sensitivity screening method used by the authors (based on the IDEXX) reliably correlates with immunohistochemically demonstrated protease sensitivity across a range of molecular subtypes and offers a generic insight into the overall protease sensitivity of the population of abnormal PrP conformers present. This will help obviate concerns that the IDEXX may be selecting abnormal PrP of differing protease sensitivity peculiar to each molecular subtype perhaps simply based on differences in PrP conformations in each of the subtypes. In addition, given the enhanced protease sensitivity and likely differences in conformation of the abnormal PrP in their case, the IDEXX may be over-estimating protease sensitivity because epitopes or chemically reactive sites important for reacting with the binding polymer may be lost even though residual, truncated, protease resistant fragments remain but are unbound by the plate.

3) At first looK, the western blot shown in Figure 3A appears of poor quality due to technical reasons rather than demonstrating a genuine “extremely irregular migrating profile” of PrP. Therefore before accepting this, I need to be reassured that this was a reproducible finding using freshly prepared homogenates from the same brain regions (not just re-using the same 20% homogenates). Otherwise the blot appears uninterpretable; how do the authors explain the PrP in other blots from the same brain regions (e.g., Figure 3C and D) resolving normally on western blots?

Minor essential revisions:

a) The lack of positive investigation findings is important and underscores the uniqueness of the case; this requires more comment. Also, did MRI include FLAIR and DWI?: if so, this should be explicitly stated.

b) What focal neurological signs did the patient exhibit; these are not described?

c) Supplementary information concerning western blot technique was not supplied.

d) Spelling mistakes: “august”; “glycosylated” throughout the manuscript.

e) The authors report that there was “minimal spongiform degeneration with larger vacuoles” in the “protease-sensitive prionopathy” cases reported by Gambetti et al, whereas the latter report clearly states “SD and astrogliosis of moderate severity”, and vacuoles were only slightly (non-significant statistically) larger.

f) With sampling areas assessed, the authors state “corpus striatum” and “caudate nucleus”; this appears to be a mistake.

g) The authors need to comment on the “microgliosis” as this appears excessive to what is generally reported in sCJD.

h) There are many instances of poor quality English grammar. In addition “y” is often used instead of “and”.

i) The antibody in Gambetti et al. is “1E4” not “1F4”.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.