Autoantibodies against the prion protein in individuals with PRNP mutations

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Study objective
To determine whether naturally occurring autoantibodies against the prion protein (PrP\textsuperscript{C}) are present in individuals with pathogenic PRNP prion disease mutations and controls, and if so, whether they are protective against prion disease.

What is known and what this paper adds
Antibodies against certain PrP\textsuperscript{C} epitopes may be neuroprotective. This study did not find elevated anti-PrP\textsuperscript{C} autoantibodies in PRNP mutation carriers, making a disease-modifying role of humoral anti-PrP\textsuperscript{C} autoimmunity unlikely.

Participants and setting
For this case-control study, blood samples were collected from 124 individuals with various pathogenetic PRNP mutations (64.5\% female; mean age, 49.3 ± 16.5 [s.d.] years) and 78 control individuals (47.4\% female; mean age, 42.8 ± 13.9 [s.d.] years) who had a family history of genetic prion disease but did not have known pathogenetic PRNP mutations. The investigators obtained these samples through international patient organizations and prion disease reference centers.

Design, size, and duration
Antibody reactivity was measured using a newly developed sandwich ELISA assay for the detection of human IgG\textsubscript{1-4} antibodies against wild-type human prion protein. Multivariate linear regression models were constructed to analyze the primary outcomes. Robustness of results was examined in matched cohorts.

Primary outcome measures
The primary outcome was comparisons of autoantibody reactivity between (a) PRNP mutation carriers and wild-type individuals (b) PRNP mutation carriers with and without clinical signs of prion diseases.

Main results and the role of chance
Antibody reactivity to PrP\textsuperscript{C} was similar between PRNP mutation carriers and wild-type controls (\(p = 0.61\), Table). Autoantibody levels were not influenced by specific PRNP mutation status nor clinical manifestation of prion disease. Post hoc analyses showed anti-PrP\textsuperscript{C} autoantibody titers to be independent of personal history of autoimmune disease and other immunological disorders, as well as PRNP codon 129 polymorphism.

Bias, confounding, and other reasons for caution
The present study tested for autoantibodies against full-length, wild-type, recombinant human PrP\textsuperscript{C} but did not test for autoantibodies against mutated PrP\textsuperscript{C} or its scrapie conformer PrP\textsuperscript{Sc}.

Study funding/potential competing interests
This study was funded by the UK, EU, French, Swiss and US governments; the Frances and Augustus Newman Foundation; and the Prion Alliance. Some authors report additional competing interests. Go to Neurology.org/N for full disclosures.

Table: Effect of PRNP mutation and clinical signs of prion disease on anti-PrP\textsuperscript{C} autoantibody reactivity

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Adjusted ( \beta ) coefficient (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRNP mutation</td>
<td>0.92 (0.70–1.20)</td>
</tr>
<tr>
<td>Clinical signs of prion disease</td>
<td>0.94 (0.61–1.46)</td>
</tr>
</tbody>
</table>

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The corresponding author(s) of the full-length article and the journal editors edited and approved the final version.
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