Brief communication

A nonsense mutation in PRNP associated with clinical Alzheimer's disease

Rita Guerreiro a,1, José Brás a,1, Aleksandra Wojtas b, Rosa Rademakers b, John Hardy a,*, Neill Graff-Radford b,c

a Department of Molecular Neuroscience, UCL Institute of Neurology, University College London, London, England
b Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA
c Department of Neurology, Mayo Clinic, Jacksonville, FL, USA

Article info

Article history:
Received 21 March 2014
Received in revised form 15 May 2014
Accepted 21 May 2014
Available online 27 May 2014

Keywords:
Alzheimer's disease
Prion
PRNP
Nonsense mutation
Exome sequencing

Abstract

Here, we describe a nonsense haplotype in PRNP associated with clinical Alzheimer's disease. The patient presented an early-onset of cognitive decline with memory loss as the primary cognitive problem. Whole-exome sequencing revealed a nonsense mutation in PRNP (NM_000311, c.C478T; p.Q160*; rs80356711) associated with homozygosity for the V allele at position 129 of the protein, further highlighting how very similar genotypes in PRNP result in strikingly different phenotypes.

1. Introduction

Alzheimer's disease (AD) is a complex disorder with some cases known to be caused by mutations in 3 genes: the amyloid precursor protein (APP), Presenilin 1 (PSEN1), and Presenilin 2 (PSEN2). The Apolipoprotein E E4 allele increases the risk of AD by 3- to 15-fold, although several genetic loci (CLU, PICALM, CR1, BIN1, MS4A, CD2AP, CD33, EP2A1, ABCA7, CD2AP, HLA-DRB5/DRB1, SORL1, PTK2B, SLC24A4, ZCWPW1, CELF1, FERM2, CASS4, INPP5D, MF22C, NME8) have a low effect on disease risk (Guerreiro et al., 2013a). More recently, the application of exome sequencing to large cohorts of AD cases and healthy controls led to the identification of rare heterozygous variants in TREM2 and PLD3 as medium effect risk factors for the disease (Cruchaga et al., 2013; Guerreiro et al., 2013b; Jonsson et al., 2013).

The application of this technology to the study of small families and individual cases with different forms of dementia has also resulted in the association of unexpected molecular causes to different clinical phenotypes (for a review see, Guerreiro et al., 2014). For example, TREM2 homozygous mutations, known to be the cause of Nasu-Hakola disease, were recently found to also cause frontotemporal dementia with no associated bone phenotypes (Guerreiro et al., 2013c); homozygous mutations in ATP13A2 (a gene known to cause Kufor-Rakeb) and GRN (where heterozygous mutations cause frontotemporal dementia) were identified in families with neuronal ceroid-lipofuscinosis (Bras et al., 2012a; Smith et al., 2012). Exome sequencing has now allowed the identification of the genetic causes of disease in cases that otherwise would have never been screened for mutations in the implicated genes because of their atypical phenotypes, but has also uncovered common biological pathways between different clinical entities (Bras et al., 2012b).

Here, we describe one more of these cases: a patient clinically diagnosed with AD found by exome sequencing to harbor a nonsense mutation in the PRNP gene.

2. Methods

When genetic tests for APP, PSEN1, and PSEN2 revealed no mutations, the patient was included in a whole-exome sequencing study. Genomic DNA was prepared according to Illumina's TruSeq Sample Preparation v3 (Illumina, CA, USA) and capture was performed with Illumina's TruSeq Exome
Table 1
Main characteristics of cases reported in the literature with PRNP nonsense mutations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>M129V poly</th>
<th>Gender</th>
<th>Origin</th>
<th>AAO (y)</th>
<th>AAD (y)</th>
<th>Clinical features</th>
<th>Pathology features</th>
<th>Presence of diarrhea</th>
<th>Family history</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y145* (rs80356710)</td>
<td>F</td>
<td>Japanese</td>
<td>38</td>
<td>59</td>
<td>Alzheimer type clinical course</td>
<td>Many amyloid plaques (PrP) and diffuse neuropil threads of paired helical filaments</td>
<td>Kitamoto et al. (1993)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y145* (rs80356710) probably the same case described by Kitamoto et al.</td>
<td>M/M</td>
<td>Japanese</td>
<td>38</td>
<td>59</td>
<td>Slowly progressive dementia</td>
<td>Severe diffuse atrophy of the cerebral and dilation of the lateral ventricles; amyloid deposits in parenchymal and leptomeningeal blood vessels and in the perivascular neuropil; neurofibrillary lesions “Family history is not contributory”</td>
<td>Ghetti et al. (1996)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q160* (rs80356711)</td>
<td>Proband: M/M; Brother: M/V (mutation on the M allele)</td>
<td>Austrian</td>
<td>Proband: 32; Brother: 48</td>
<td>Slowly progressive dementia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q160* (rs80356711)</td>
<td>Proband: M/V; Mother: M/M</td>
<td>F</td>
<td>Proband: 39; Mother: 59</td>
<td>The clinical and initial pathologic features in both patients were strongly suggestive of AD</td>
<td>Proband: abundant limbic and neocortical neuritic plaque-like structures and NFTs, consistent with a neuropathologic diagnosis of AD. Immunohistochemical studies: PrP immunopositive deposits. Mother: severe neurofibrillary tangles and neuritic plaque pathology in frontal cortex and hippocampus. Classic Lewy bodies and alpha-synuclein immunopositive inclusions and neurites.</td>
<td>Nothing noted in the proband but present in the mother</td>
<td></td>
<td>Jayadev et al. (2011)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y163*</td>
<td>Mutation in the V allele</td>
<td>Fourth decade with cognitive problems and seizures starting on the fifth and sixth decade</td>
<td>Average of 57 (range 40 – 70)</td>
<td>Chronic diarrhea with autonomic failure and a length-dependent axonal, predominantly sensory, peripheral polyneuropathy.</td>
<td>PrP-amyloid deposition was seen throughout the peripheral organs, including the bowel and peripheral nerves. Neuropathologic examination at end stage demonstrated PrP deposition in the form of frequent cortical amyloid plaques, cerebral amyloid angiopathy, and tauopathy. A unique pattern of abnormal PrP fragments was seen in brain tissue.</td>
<td>Yes</td>
<td>Dominant trait</td>
<td>Mead et al. (2013)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y163* probably the same family reported by Mead S, et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><a href="http://dx.doi.org/10.1136/jnnp.2010.226340.31">http://dx.doi.org/10.1136/jnnp.2010.226340.31</a></td>
</tr>
<tr>
<td>Y163* probably the same case as reported in previous entrance and by Mead, S et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9 patients from 1 family</td>
<td>Revesz et al. (2009)</td>
</tr>
</tbody>
</table>

(continued on next page)
Table 1 (continued)

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Gender</th>
<th>Origin</th>
<th>AAO (y)</th>
<th>AAD (y)</th>
<th>Clinical features</th>
<th>Pathology features</th>
<th>Presence of diarrhea</th>
<th>Family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y226* M/V</td>
<td>F</td>
<td>Dutch</td>
<td>54</td>
<td></td>
<td>Dementia, visual, sensory neuropathy, and cognitive impairment</td>
<td>PrP amyloid deposits, neurofibrillary tangles, and abundant neuritic plaques involved in white matter and the absence of PrP-CAA.</td>
<td>No diarrhea available</td>
<td>Mother, maternal grandfather (frequent diarrhea and weight lost)</td>
</tr>
<tr>
<td>Q227*</td>
<td>F</td>
<td>Dutch</td>
<td>39</td>
<td></td>
<td>Clinically diagnosed with FTD</td>
<td>PrP amyloid deposits, focal neurofibrillary tangles, and some spongiosis in the cerebral gray matter and the absence of PrP-CAA.</td>
<td>No diarrhea available</td>
<td>Father, mother (diagnosed based on the same haplotype)</td>
</tr>
<tr>
<td>V28*</td>
<td>F</td>
<td>Dutch</td>
<td>39</td>
<td></td>
<td>Clinically diagnosed with PTLD</td>
<td>PrP amyloid deposits, focal neurofibrillary tangles, and some spongiosis in the cerebral gray matter and the absence of PrP-CAA.</td>
<td>No diarrhea available</td>
<td>Father, maternal grandfather (diagnosed based on the same haplotype)</td>
</tr>
</tbody>
</table>

Key: AAD, age at death; AAO, age at onset; AD, Alzheimer’s disease; F, female; FTD, frontotemporal dementia; M, male; Poly, polymorphism; NFTs, neurofibrillary tangles; y, years.

Further inspection of the 9423 coding variants found (445 of which were novel), revealed a nonsense mutation in PRNP (NM_000311, c.C478T; p.Q160*) associated with homozygosity for the V allele at position 129 of the protein.

The patient was followed in the Mayo Clinic and presented an early-onset of cognitive decline at 38 years with memory loss as the primary cognitive problem, but also showing an impulsive behavior on her neuropsychological assessment. Her mother had a similar problem, also of early onset (no DNA was available for testing). Her maternal grandparents lived long and were said not to be affected. Her brother and daughter were also unaffected at the time of evaluation. She had temporary diarrhea, which was thought to be related to the introduction of Aricept, and her positron emission tomography scan showed left frontal hypometabolism. The patient was diagnosed with clinical AD and no neuropathologic assessment was possible.

4. Discussion

The mutation here described (p.Q160*) has been previously reported in 2 other cases (Table 1) diagnosed with an Alzheimer-like dementia. The first case did not have a detailed clinical description and no pathologic findings were reported (Finckh et al., 2000). The second case was deeply phenotyped, and neuropathologic evaluation showed abundant limbic and neocortical neuritic plaque-like structures and neurofibrillary tangles consistent with a neuropathologic diagnosis of AD. Immunohistochemical studies also demonstrated PrP immunopositive deposits (Jayadev et al., 2011).

In the literature, 6 different mutations in PRNP leading to a premature truncation of the protein can be found (Table 1). None of these cases was initially diagnosed with a prion disease. In fact, the proband’s mother in the report by Jayadev et al. (2011) was also neuropathologically diagnosed as AD before immunohistochemical studies were performed.

Recently, Mead et al. (2013) described an unusual phenotype associated with a novel nonsense mutation in PRNP. The affected members of this family carried the p.129V-163* PRNP truncation haplotype and developed autonomic failure with chronic diarrhea and peripheral polyneuropathy in adulthood.

The different truncating mutations in PRNP appear to have some common features namely: prolonged clinical courses, atypical for prion diseases, severe neurofibrillary tangle pathology, and high levels of cerebral amyloidosis. However, it is remarkable that the simple removal of an extra 3 amino acids on the same haplotype (V129 background), consistently results in a very different
phenotype: truncated PRNP at amino acids 160 or 163 present with a clear hippocampal involvement or an autonomic defect, respectively.

Disclosure statement

The authors declare no competing financial or personal interests that can influence the presented work.

Acknowledgements

This work was supported by the Alzheimer’s Research UK and by an anonymous donor. It was also supported in part by the Wellcome Trust and/or MRC Joint Call in Neurodegeneration award (WT089698) to the UK Parkinson’s Disease Consortium whose members are from the University College London/Institute of Neurology, the University of Sheffield, and the MRC Protein Phosphorylation Unit at the University of Dundee, the National Institutes of Health/National Institute on Aging P50-AG016574 grant and by a fellowship from Alzheimer’s Research UK to Dr. Guerreiro.

References


