Variant CJD in an individual heterozygous for *PRNP* codon 129

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Lancet 2009; 374: 2128

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A 30-year-old man was admitted to hospital in June, 2008, with a 13-month history of personality change, progressive unsteadiness, and intellectual decline. He complained of severe leg pain and poor memory. 2 months later he developed visual hallucinations and falsely believed he had an abdominal tumour. Symptoms worsened over the next 3 months. In October, 2008, his score on the mini mental state examination was 26/30. Pursuit eye movements were saccadic. He had a pout reflex. There was mild ataxia in the arms. His legs were severely ataxic with brisk tendon reflexes and a left extensor plantar response. He needed two crutches to walk. Medical history included tonsillectomy and removal of a cervical lymph node 15 years previously but he had never had a blood transfusion or received implantation of other human tissues.

EEG showed slow wave activity. CSF protein, glucose, and cell count were normal but the 14-3-3 protein was positive. MRI of the brain was consistent with the pulvinar sign (figure A). Although not all neuroradiologists consulted considered the pulvinar sign positive, quantitative assessment showed symmetrical higher signal in the pulvinar nuclei than the caudate nuclei (figure B). Extensive screens for genetic, metabolic, and autoimmune diseases, including those induced by neoplasia, were negative. *PRNP* analysis did not show any known disease-associated mutations; codon 129 was heterozygous. A clinical diagnosis of variant Creutzfeldt-Jakob disease (vCJD) was made on the basis of a characteristic clinical onset and progression, exclusion of other diagnoses, and MRI findings. Sporadic CJD was judged unlikely given the combination of young age, clinical features, MRI findings, and absence of pseudoperiodic complexes on EEG. His carers did not want further investigation. His condition deteriorated and he died in January, 2009. Autopsy was not done.

Human prion diseases have acquired, sporadic, and inherited aetiologies, show wide phenotypic heterogeneity, and are associated with propagation of infectious prions of many distinct strain types.[1] Since 1994, about 200 cases of vCJD, causally related to exposure to bovine spongiform encephalopathy (BSE) prions, have been identified worldwide. vCJD is generally seen in young adults, has characteristic neuropathological features and tissue distribution of infectivity, and a distinctive type 4 (London classification) molecular strain type.[1] A polymorphism at codon 129 (encoding methionine or valine) of the human prion protein gene (*PRNP*), constitutes a powerful susceptibility factor in all types of prion disease. In vCJD, every case genotyped to date has been methionine homozygous. In the other acquired prion diseases, cases have occurred in all genotypes but with different mean incubation periods,[1] which can span decades;[2] *PRNP* codon 129 heterozygotes generally have the longest incubation periods. There is a report of a recipient of a blood transfusion from a donor incubating vCJD who died of unrelated causes but showed signs of prion infection at autopsy and was *PRNP* codon 129 heterozygous.[3] Animal studies have suggested that different clinicopathological phenotypes could occur in people with various *PRNP* codon 129 genotypes.[4,5] The majority of the UK population have potentially been exposed to BSE prions but the extent of clinically silent infection remains unclear. About a third of the UK population are *PRNP* codon 129 methionine homozygous. If individuals with other genotypes are similarly susceptible to developing prion disease after BSE prion exposure, but with longer incubation periods, further cases, which may or may not meet diagnostic criteria for vCJD, would be expected in these *PRNP* codon 129 genotypes. However, prion disease susceptibility and incubation periods are also affected by other genetic loci, and the possibility remains that cases of vCJD to date may have unusual combinations of genotypes at these loci, yet to be fully characterised.

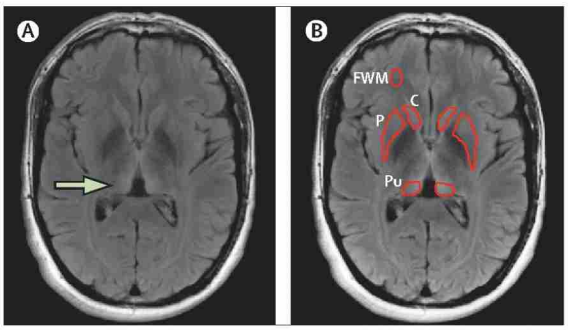

Figure: MRI
(A) Increased signal intensity in the pulvinar nucleus bilaterally (arrow). (B) MR signal intensity in the pulvinar (Pu) is higher than in the head of the caudate nuclei (C), putamen (P), and right frontal white matter (FWM).

Contributors
All authors were involved in discussion about diagnosis, care of the patient, and preparation of the report. Written consent to publish was obtained.

Conflicts of interest
JC is a director and shareholder of D-Gen Ltd, an academic spin-out company in the field of prion disease diagnosis, decontamination, and therapy. The other authors declare that they have no conflicts of interest.

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