Why do people get CJD?

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University of Edinburgh
UK
Creutzfeldt-Jakob Disease
(Spongiform Encephalopathy):
Transmission to the Chimpanzee

We believe that Creutzfeldt-Jakob disease has been experimentally transmitted to the chimpanzee, and that the disease is caused by a transmissible agent.

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EuroCJD: CJD deaths 1993-2012
(n = 11,440)
Sporadic CJD
COUNTRIES IN WHICH CJD HAS BEEN REPORTED
EUROCJD Members

Sporadic CJD

Annual Mortality Rates to 2011:
Mean for period of surveillance (8-19 years)
DISTRIBUTION OF SPORADIC CJD IN THE UK: 1990-2002
England and Wales

W. B. MATTHEWS

From the University Department of Neurology, Churchill Hospital, Oxford

SYNOPSIS Some aspects of the epidemiology of Creutzfeldt-Jakob disease in England and Wales in the decade 1964–73 were studied with the object of detecting evidence of natural transmission of this slow virus encephalopathy. Some geographical clustering and possibility of contact between cases was found.

FIG. 1 Sketch map of cluster of cases of CJD in a rural area. Shading represents villages. The lettering is explained in the text.
Enhanced geographically restricted surveillance simulates sporadic Creutzfeldt-Jakob disease cluster

Genevieve M. Klug, Handan Wand, Alison Boyd, Matthew Law, Scott Whyte, John Kaldor, Colin L. Masters and Steven Collins

Brain 2009: 132; 493-501
Creutzfeldt-Jakob disease in a husband and wife

P. Brown, MD, L. Cervenáková, MD, L. McShane, PhD, L. G. Goldfarb, MD, K. Bishop, BS, F. Bastian, MD, J. Kirkpatrick, MD, P. Piccardo, MD, B. Ghetti, MD and D. C. Gajdusek, MD

ABSTRACT

A 53-year-old man died of sporadic Creutzfeldt-Jakob disease (CJD) after a 1.5-year clinical course. Four and a half years later, his then 55-year-old widow died from CJD after a 1-month illness. Both patients had typical clinical and neuropathologic features of the disease, and pathognomonic proteinase-resistant amyloid protein ("prion" protein, or PrP) was present in both brains. Neither patient had a family history of neurologic disease, and molecular genetic analysis of their PrP genes was normal. No medical, surgical, or dietary antecedent of CJD was identified; therefore, we are left with the unanswerable alternatives of human-to-human transmission or the chance occurrence of sporadic CJD in a husband and wife.
That calculation yields $r = 1.8$ per million sporadic CJD deaths per year. Using the values of $c_1, c_2, \ldots, c_{16}$ and $r$ calculated from the above table, we compute $1 - p_1 \cdot p_2 \cdot \ldots \cdot p_{16}$ to be $0.021$. That is, if we observe a population of similar size and marital status composition to the U.S. population from 1979 to 1994, we estimate a $2.1\%$ chance of observing a married couple in which both husband and wife die of sporadic CJD within 5 years of one another.
Graphical representation of selected results.

M = Months;
y = years;
o. = onset;
b.o. = Before onset;
adj. = adjusted.
Health professions and risk of sporadic Creutzfeldt-Jakob disease, 1965 to 2010

E Alcalde-Cabero, J Almazán-Isla, J P Brandel, M Breithaupt, J Catarino, S Collins, J Haybäck, R Höftberger, E Kahana, G G Kovacs, A Ladogana, E Mitrova, A Molesworth, Y Nakamura, M Pocchiari, M Popovic, M Ruiz-Tovar, A L Taratuto, C van Duijn, R G Will, I Zerr, J de Pedro Cuesta (jpedro@isciii.es)

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17. Neurology Department, Kanazawa University Hospital, Kanazawa, Japan

Euro Surveillance 2012;17(15) pii=20144
We conclude that a wide spectrum of medical specialities and health professions are represented in sCJD cases and that the data analysed do not support any overall increased occupational risk for health professionals.
Mortality rates for definite and probable sporadic CJD in the UK
1 January 1990 - 31 December 2014

1 case/million/year

0.5 case/million/year

14-3-3

MRI

RTQuIC
Number of definite and probable TSE cases and age standardised mortality rate in Australia, 1970 to 2012, by classification and year
Sporadic CJD

- No environmental risk factors for sCJD have been identified
- No link to occupation, past medical history, blood transfusion, medications, diet, etc.
- No link to scrapie in sheep
- No evidence of spread from person to person
- Cases occur randomly in space and time and occur worldwide
Sporadic CJD

• These.... studies suggest that at some point in the lives of the one in a million individuals who acquire sporadic Creutzfeldt-Jakob disease, cellular PrP may spontaneously convert to the scrapie form.

• Stanley Prusiner 1995
Genetic human prion disease
Linkage of a prion protein missense variant to Gerstmann–Sträussler syndrome

Karen Hsiao*, Harry F. Baker‡, Tim J. Crow‡,
Mark Poulter‡, Frank Owen‡,
Joseph D. Terwilliger§, David Westaway*,
Jurg Ott§ & Stanley B. Prusiner*‡¶
## MUTATIONS OF THE PRP GENE UK

*(n=188)*

<table>
<thead>
<tr>
<th>MUTATION</th>
<th>NUMBER</th>
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<tr>
<td>Insertions in the coding region of the PrP gene</td>
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<tr>
<td>E200K</td>
<td>44</td>
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<tr>
<td>P102L</td>
<td>37</td>
</tr>
<tr>
<td>D178N</td>
<td>14</td>
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<tr>
<td>A117V</td>
<td>13</td>
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<tr>
<td>V210I</td>
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<tr>
<td>Q212P</td>
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<tr>
<td>Y163X</td>
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<tr>
<td>D167G</td>
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<td>G54S</td>
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<td>P105L</td>
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<td>P84S</td>
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<td>S132I</td>
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Quantifying prion disease penetrance using large population control cohorts

by Eric Vallabh Minikel, Sonia M. Vallabh, Monkol Lek, Karol Estrada, et al

Sci Transl Med
Volume 8(322):322ra9-322ra9
January 20, 2016
Fig. 3. Variants that confer intermediate amounts of lifetime risk.

<table>
<thead>
<tr>
<th>Variant(s)</th>
<th>Ancestry</th>
<th>Comparison (allele frequencies)</th>
<th>Lifetime risk (95% CI)</th>
<th>Positive family history in cases</th>
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<tbody>
<tr>
<td>M232R</td>
<td>Japanese</td>
<td>Cases (2.2%) vs. ExAC (0.38%)</td>
<td>3%</td>
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<td></td>
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<td>Cases (2.2%) vs. 23andMe (0.54%)</td>
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<td></td>
</tr>
<tr>
<td>V180I</td>
<td>Japanese</td>
<td>Cases (7.2%) vs. ExAC (0.15%)</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cases (7.2%) vs. 23andMe (&lt;0.094%*)</td>
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<tr>
<td>V210I</td>
<td>Italian</td>
<td>Cases (8.1%) vs. ExAC (0.021%)</td>
<td>12%</td>
<td></td>
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<td>P102L</td>
<td>Global</td>
<td>Cases (4.9%) vs. ExAC (0%)</td>
<td>49% (E200K)</td>
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</tr>
<tr>
<td>A117V</td>
<td></td>
<td></td>
<td>70% (GSS†)</td>
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<td>D178N</td>
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<td></td>
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<tr>
<td>E200K</td>
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<td></td>
<td>88% (FFi†)</td>
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</table>

Population baseline risk

Complete penetrance

Eric Vallabh Minikel et al., Sci Transl Med 2016;8:322ra9

Published by AAAS
Discordant Gerstmann-Sträussler-Scheinker disease in monozygotic twins

Shinji Hamasaki, Susumu Shirabe, Ryouichi Tsuda, Toshiro Yoshimura, Tatsufumi Nakamura, Katsumi Eguchi

THE LANCET • Vol 352 • October 24, 1998

Family pedigree

- Probably affected
- Affected
- P102L mutation detected
- Proband
Seven-year discordance in age at onset in monozygotic twins with inherited prion disease (p102L)

*Neuropathology and Applied Neurobiology* (2009), **35**, 427–432

T. Webb*†
S. Mead*†
J. Beck†
J. Uphill†
S. Pal*†
S. Hampson*
J. D. F. Wadsworth†
I. Dalmau Mena†
C. O’Malley†
S. Wroe*†
A. Schapira‡
S. Brandner†
J. Collinge*†
Genetic Prion Disease

• We suspect that mutation in the PrP gene render the resulting proteins susceptible to flipping from an alpha-helical to a beta-sheet shape. Presumably, it takes time until one of the molecules spontaneously βips over and still more time for scrapie PrP to accumulate and damage the brain enough to cause symptoms.

• Stanley Prusiner 1995
iatrogenic CJD
Incubation periods and clinical presentations of iatrogenic Creutzfeldt-Jakob disease, according to source of infection

<table>
<thead>
<tr>
<th>Source of Infection</th>
<th>No. cases</th>
<th>Mean incubation period, y (range)</th>
<th>Clinical signs†</th>
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</thead>
<tbody>
<tr>
<td>Dura mater graft</td>
<td>228</td>
<td>12 (1.3–30)</td>
<td>Cerebellar, visual, dementia</td>
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<tr>
<td>Neurosurgical instruments§*</td>
<td>4</td>
<td>1.4 (1–2.3)</td>
<td>Visual, dementia, cerebellar</td>
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<tr>
<td>Stereotactic EEG needles</td>
<td>2</td>
<td>1.3, 1.7</td>
<td>Dementia, cerebellar</td>
</tr>
<tr>
<td>Corneal transplant</td>
<td>2</td>
<td>1.5, 27</td>
<td>Dementia, cerebellar</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>226</td>
<td>17 (5–42)‡</td>
<td>Cerebellar</td>
</tr>
<tr>
<td>Gonadotropin</td>
<td>4</td>
<td>13.5 (12–16)</td>
<td>Cerebellar</td>
</tr>
<tr>
<td>Packed red blood cells§</td>
<td>3</td>
<td>6.5, 7.8, 8.3</td>
<td>Psychiatric, sensory, dementia, cerebellar</td>
</tr>
</tbody>
</table>

*EEG, electroencephalogram.
†In order of decreasing frequency.
‡Averages and ranges were 13 (5–24) y in France; 20 (7–39) y in the United Kingdom; and 22 (10–42) y in the United States.
§An additional asymptomatic but infected red-cell recipient died of an unrelated illness; another asymptomatic infected hemophilia patient who had been exposed to potentially contaminated factor VIII also died of an unrelated illness (neither is included in the table).
Annual incidence of variant Creutzfeldt-Jakob disease (vCJD) caused by ingestion of meat products contaminated with bovine spongiform encephalopathy agent (A) and iatrogenic CJD caused by contaminated dura mater (B) and cadaveric human growth hormone (C), 1982-2011.
Variant CJD
vCJD CASES BY YEAR AND COUNTRY
1994-2017 (n=230)

Number
Year of Death
Taiwan
Spain
Portugal
Netherlands
Japan
Saudi Arabia
Italy
Canada
USA
Ireland
France
UK

Infectious Units Entering Food supply

5 million bovine oral ID50 units entered food supply from 1980 – 2001
>99% from animals older than 30 months

(Graph based on previous infectivity value – 10 x higher)

Base case with 3 months test sensitivity