SUPPLEMENTAL INFORMATION

Quantifying penetrance in a dominant disease gene using large population control cohorts

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Supplementary Discussion

Additional variants

Of the 63 reportedly pathogenic variants (Table S2), 10 are discussed in the main text. Of those 10, our data and our analysis of the literature indicate high penetrance for 4 (P102L, A117V, D178N, and E200K), intermediate penetrance for 3 (V180I, V210I, and M232R), and suggest that 3 others may be benign (P39L, E196A, and R208C). In this section we discuss four additional variants that we cannot conclusively reclassify but which are unlikely to be highly penetrant, and we also provide a brief discussion of interpretation for remaining variants.

**R148H** has been reported in a two isolated patients with a sporadic Creutzfeldt-Jakob disease phenotype and negative family history (1, 2) and appears one additional time in our case cohorts (Table S1). Based on its rarity in cases, lack of familial segregation and presence on 3 alleles in ExAC, it is unlikely to be a highly penetrant Mendelian variant. It might be benign or it might slightly increase prion disease risk.

**T188R** has been reported in two cases in the literature. One German individual presented with a sporadic Creutzfeldt-Jakob disease phenotype but no autopsy was performed; family history was negative (3, 4). One Mexican-American individual had autopsy-confirmed prion disease and an ambiguous family history (5). This variant appears 12 times in our case cohort (all in the United States) and 3 times in ExAC (all in Latino populations). Based on its allele frequency in controls, rarity in cases and lack of any clear evidence for segregation in families, T188R is unlikely to be a highly penetrant Mendelian disease variant. It is not clear whether it is benign or increases prion disease risk.

**V203I** has been reported in three heterozygous patients - one Italian (6), one Korean (7), and one Chinese (8), as well as in one Japanese homozygote (9). Family history is negative in all of these reported patients as well as in two additional V203I cases in our Japanese case cohort (Table S10). In our cohorts, this variant appears in a total of 16 cases from several countries; in ExAC, it appears in 3 European individuals. Based on its allele frequency in controls, rarity in cases and lack of any clear evidence for segregation in families, V203I is unlikely to be a highly penetrant Mendelian disease variant, and could be benign or could increase prion disease risk. The report of prion disease in a V203I homozygote makes us slightly inclined to favor the interpretation that V203I does increase prion disease risk.

**R208H** has been reported in several isolated cases of varied ancestries, all with a negative family history (10–16). In our cohorts, it appears in 13 prion disease cases, 9 ExAC individuals and 22 individuals in the 23andMe database. Given its high frequency in controls, this variant may be benign or may slightly increase prion disease risk.
Other variants. Excluding variants discussed in the main text and above, 0.8% (87 / 10460) of individuals in our case series harbor other rare PRNP missense variants, some of which have been reported as pathogenic (Table S2) and others of which have not. Because most of these variants are very rare both in cases and in population controls, comparisons of case and control allele frequency are not well powered to evaluate the pathogenicity of most individual variants. Collectively, our data indicate that this category includes at least some variants that increase prion disease risk, because only 0.3% (187 / 60706) of ExAC individuals harbor a rare missense variant other than those discussed in the main text or above, whereas 0.8% (87 / 10460) of prion disease cases harbor one of these variants, a significant enrichment (p = 1 × 10^{-12}, Fisher's exact test). Indeed, Mendelian segregation has been demonstrated for some of these variants, such as T183A and F198S (17, 18). However, the fact that, in the aggregate, we observe only modest (~3-fold) enrichment of such variants in cases versus controls suggests that this category also includes many neutral or very low-risk variants, consistent with our expectation that sporadic prion disease cases should, by chance, harbor some rare variants unassociated with disease. We also cannot exclude the possibility that some specific rare variants, particularly those observed in controls and not in cases, could be protective.

Future novel missense variants. Additional novel missense variants in PRNP are sure to be observed in prion disease patients in the future. Our findings that some reportedly pathogenic variants are either benign or exhibit low penetrance, together with our observation that ~4 in 1000 controls harbor a rare PRNP missense variant, urge caution in the interpretation of novel variants in prion disease patients. This is consistent with current guidelines (19, 20), which indicate that novel protein-altering variants, even in established disease genes, should not be assumed to be causal or highly penetrant until evidence, such as Mendelian segregation, or significant enrichment in cases over controls, can be established.

Dominant versus allelic models

Virtually all patients ever reported with genetic prion disease have been heterozygous for the putative pathogenic variants. Five individuals homozygous for E200K (21) were reported to have a younger age of onset than heterozygotes (mean 50 vs. 59 years, p = .03), suggesting some degree of codominance. There have been individual case reports of homozygotes for Q212P (22) and V203I (9), both without a family history among heterozygote relatives, which might suggest that dosage of the mutant allele is important. We are not aware of any other reports of individuals homozygous for potentially pathogenic variants in PRNP. Regardless of whether a dominant or allelic model is assumed, our formula for lifetime risk (Materials and Methods) gives identical point estimates of penetrance and virtually identical 95% confidence intervals.
Table S1. Allele counts of rare PRNP variants in 16,025 definite and probable prion disease cases in 9 countries.

Abbreviations: OPRD, octapeptide repeat deletion; OPRI, octapeptide repeat insertion. *V203I in Japan: two heterozygotes and one homozygote, four alleles total. All other individuals are heterozygotes.

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### Table S2. Rare PRNP variants reported in peer-reviewed literature to cause prion disease

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Table S3. Allele counts of rare PRNP variants in 60,706 individuals in ExAC.

Chromosomal positions are given in GRCh37 coordinates and HGVS notations are given relative to Ensembl transcript ENST00000379440. Mean read depth across the PRNP coding sequence was 55.21. Call rate is the proportion of ExAC individuals with a genotype call of genotype quality (GQ) ≥20 and a depth (DP) of ≥10 reads.

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<td>c.606</td>
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<td>c.607</td>
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<td>c.604</td>
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<td>c.635</td>
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Table S4. Summary of rare PRNP variants by functional class in ExAC

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<th>Class</th>
<th>Total AC</th>
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<td>missense</td>
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<td>nonsense</td>
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<td>read-through</td>
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<td>synonymous</td>
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Table S5. Allele counts of 16 reportedly pathogenic PRNP variants in >500,000 23andMe research participants.

To protect the privacy of 23andMe research participants, allele count (AC) values between 1 and 5 inclusive are displayed as “1-5” and are rounded up to 5 for the purposes of plotting. These alleles were seen almost exclusively in a heterozygous state, with fewer than 5 homozygous individuals total across all 16 variants.

<table>
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<tr>
<th>Variant</th>
<th>dbSNP id</th>
<th>23andMe id</th>
<th>Called genotypes</th>
<th>AC</th>
<th>Comments</th>
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<tr>
<td>P102L</td>
<td>rs74315401</td>
<td>i5004359</td>
<td>502075</td>
<td>1-5</td>
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<tr>
<td>Gene</td>
<td>rs Number</td>
<td>i500435X</td>
<td>501XX</td>
<td>AC=XX in YY individuals with &gt;90% Japanese ancestry</td>
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<td>---------------------------------------------------</td>
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<td>rs28933385</td>
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</tr>
<tr>
<td>M232R</td>
<td>rs74315409</td>
<td>i5004352</td>
<td>502475</td>
<td>78 AC=29 in 2,685 individuals with &gt;90% Japanese ancestry</td>
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<tr>
<td>V180I</td>
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<td>i5004353</td>
<td>502125</td>
<td>15 AC=1-5 in 2,670 individuals with &gt;90% Japanese ancestry</td>
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<td>V210I</td>
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<td>502290</td>
<td>13 AC=8 in 385,030 Europeans</td>
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<td>rs55826236</td>
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<td>22 AC=19 in 384,645 Europeans</td>
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</table>
Table S6. Phenotypes investigated in studies in which ExAC individuals with reportedly pathogenic *PRNP* variants were ascertained.

Note that we do not have access to phenotypic data to indicate whether a particular individual was ascertained as a case or a control. Therefore “cardiovascular” simply means an individual was ascertained in a cardiovascular disease cohort, not necessarily that the individual has cardiovascular disease. “Mixed” cohorts include controls, cardiovascular and pulmonary phenotypes.

<table>
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<tr>
<th>Cohort phenotype</th>
<th>Total in ExAC</th>
<th>Number with reportedly pathogenic <em>PRNP</em> variants</th>
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<td>Cancer</td>
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<td>Metabolic</td>
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<td>19</td>
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<td>Population controls</td>
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<td>6</td>
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<td>Psychiatric</td>
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<td>Total</td>
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Table S7. Inferred ancestry and codon 129 genotypes of ExAC individuals with reportedly pathogenic variants.

Three-letter HapMap ancestry codes are defined in Table S8.

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</tr>
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<td>1 TSI</td>
<td>1 M/V</td>
</tr>
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<tr>
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<td>1 CLM, 2 MXL</td>
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<td>Population code</td>
<td>Description</td>
<td>Super population</td>
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<td>-----------------</td>
<td>--------------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>ACB</td>
<td>African Caribbeans in Barbados</td>
<td>AFR</td>
</tr>
<tr>
<td>ASW</td>
<td>Americans of African Ancestry in SW USA</td>
<td>AFR</td>
</tr>
<tr>
<td>BEB</td>
<td>Bengali from Bangladesh</td>
<td>SAS</td>
</tr>
<tr>
<td>CDX</td>
<td>Chinese Dai in Xishuangbanna, China</td>
<td>EAS</td>
</tr>
<tr>
<td>CEU</td>
<td>Utah Residents (CEPH) with Northern and Western European ancestry</td>
<td>EUR</td>
</tr>
<tr>
<td>CHB</td>
<td>Han Chinese in Beijing, China</td>
<td>EAS</td>
</tr>
<tr>
<td>CHS</td>
<td>Southern Han Chinese</td>
<td>EAS</td>
</tr>
<tr>
<td>CLM</td>
<td>Colombians from Medellin, Colombia</td>
<td>AMR</td>
</tr>
<tr>
<td>ESN</td>
<td>Esan in Nigeria</td>
<td>AFR</td>
</tr>
<tr>
<td>FIN</td>
<td>Finnish in Finland</td>
<td>EUR</td>
</tr>
<tr>
<td>GBR</td>
<td>British in England and Scotland</td>
<td>EUR</td>
</tr>
<tr>
<td>GIH</td>
<td>Gujarati Indian from Houston, Texas</td>
<td>SAS</td>
</tr>
<tr>
<td>GWD</td>
<td>Gambian in Western Divisions in The Gambia</td>
<td>AFR</td>
</tr>
<tr>
<td>IBS</td>
<td>Iberian population in Spain</td>
<td>EUR</td>
</tr>
</tbody>
</table>

Table S8. Inferred ancestry of all ExAC individuals.

Methods for ancestry assignment are described in Materials and Methods.
Table S9. Inferred ancestry of 23andMe research participants

<table>
<thead>
<tr>
<th>Ancestry</th>
<th>Minimum called genotypes</th>
<th>Maximum called genotypes</th>
<th>Total allele count of reportedly pathogenic PRNP variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>European</td>
<td>382865</td>
<td>408475</td>
<td>≥35</td>
</tr>
<tr>
<td>Latino</td>
<td>42425</td>
<td>44480</td>
<td>≥10</td>
</tr>
<tr>
<td>African</td>
<td>22945</td>
<td>23795</td>
<td>≥10</td>
</tr>
<tr>
<td>East Asian</td>
<td>20255</td>
<td>21710</td>
<td>≥75</td>
</tr>
<tr>
<td>All others</td>
<td>30975</td>
<td>33125</td>
<td>≥20</td>
</tr>
<tr>
<td>TOTAL</td>
<td>499455</td>
<td>531575</td>
<td>141</td>
</tr>
</tbody>
</table>
Table S10. Details of Japanese prion disease cases

<table>
<thead>
<tr>
<th>Variant</th>
<th>N</th>
<th>Male/Female</th>
<th>Age at onset*</th>
<th>(range)</th>
<th>Positive family history (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insertion</td>
<td>8</td>
<td>4/4</td>
<td>51.0 ± 12.0</td>
<td>(26-68)</td>
<td>5 (63)</td>
</tr>
<tr>
<td>P102L</td>
<td>83</td>
<td>38/45</td>
<td>55.5 ± 10.3</td>
<td>(22-75)</td>
<td>69 (83)</td>
</tr>
<tr>
<td>P105L</td>
<td>12</td>
<td>7/5</td>
<td>46.9 ± 8.4</td>
<td>(31-61)</td>
<td>11 (92)</td>
</tr>
<tr>
<td>D178N-129M</td>
<td>4</td>
<td>3/1</td>
<td>54.5 ± 5.5</td>
<td>(46-61)</td>
<td>None</td>
</tr>
<tr>
<td>D178N-129V</td>
<td>1</td>
<td>1/0</td>
<td>74</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>V180I</td>
<td>218</td>
<td>84/134</td>
<td>77.4 ± 6.8</td>
<td>(44-93)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>E200K</td>
<td>63</td>
<td>30/33</td>
<td>61.1 ± 9.9</td>
<td>(31-83)</td>
<td>28 (44)</td>
</tr>
<tr>
<td>V203I</td>
<td>3</td>
<td>2/1</td>
<td>73</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>R208H</td>
<td>1</td>
<td>0/1</td>
<td>74</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>V210I</td>
<td>1</td>
<td>0/1</td>
<td>55</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>M232R</td>
<td>63</td>
<td>32/31</td>
<td>64.4 ± 10.9</td>
<td>(15-82)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>V180I+M232R</td>
<td>4</td>
<td>2/2</td>
<td>71.3 ± 3.6</td>
<td>(65-74)</td>
<td>None</td>
</tr>
</tbody>
</table>

*Age at onset is expressed as the mean ± SD (range) years.

<table>
<thead>
<tr>
<th>Variant</th>
<th>Duration**</th>
<th>(range)</th>
<th>Codon 129</th>
<th>Codon 219</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insertion</td>
<td>27.8 ± 17.7</td>
<td>(3-57)</td>
<td>MM 6; MV 1</td>
<td>EE 6; KK 1</td>
</tr>
<tr>
<td>P102L</td>
<td>48.4 ± 35.8</td>
<td>(2-186)</td>
<td>MM 67; MV 6</td>
<td>EE 70; EK 2</td>
</tr>
<tr>
<td>P105L</td>
<td>90.2 ± 40.4</td>
<td>(25-184)</td>
<td>MV 11</td>
<td>EE 7</td>
</tr>
<tr>
<td>D178N-129M</td>
<td>8.5 ± 4.4</td>
<td>(2-13)</td>
<td>MM 4</td>
<td>EE 4</td>
</tr>
<tr>
<td>D178N-129V</td>
<td>24</td>
<td>MV 1</td>
<td>EE 1</td>
<td></td>
</tr>
<tr>
<td>V180I</td>
<td>16.4 ± 14.5</td>
<td>(0-70)</td>
<td>MM 162; MV 54</td>
<td>EE 210</td>
</tr>
<tr>
<td>E200K</td>
<td>5.0 ± 6.0</td>
<td>(1-32)</td>
<td>MM 58; MV 3</td>
<td>EE 58; EK 3</td>
</tr>
<tr>
<td>V203I</td>
<td>3.7 ± 2.1</td>
<td>(1-6)</td>
<td>MM 3</td>
<td>EE 3</td>
</tr>
</tbody>
</table>
**Duration between the onset and akinetic mutism or death without akinetic mutism. Duration is expressed as the mean ± SD (range) months.**

<table>
<thead>
<tr>
<th>Variant</th>
<th>PSWCs on EEG (%)</th>
<th>Hyperintensities on MRI (%)</th>
<th>Positive 14-3-3 protein (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insertion</td>
<td>3/8 (38)</td>
<td>2/7 (29)</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>P102L</td>
<td>11/72 (15)</td>
<td>32/76 (42)</td>
<td>13/34 (38)</td>
</tr>
<tr>
<td>P105L</td>
<td>1/10 (10)</td>
<td>1/11 (9)</td>
<td>1/2 (50)</td>
</tr>
<tr>
<td>D178N-129M</td>
<td>0/4 (0)</td>
<td>1/4 (25)</td>
<td>1/2 (50)</td>
</tr>
<tr>
<td>D178N-129V</td>
<td>0/1 (0)</td>
<td>0/1 (0)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>V180I</td>
<td>19/203 (9)</td>
<td>212/213 (99)</td>
<td>110/140 (79)</td>
</tr>
<tr>
<td>E200K</td>
<td>56/63 (89)</td>
<td>56/59 (95)</td>
<td>29/31 (94)</td>
</tr>
<tr>
<td>V203I</td>
<td>3/3 (100)</td>
<td>2/2 (100)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>R208H</td>
<td>1/1 (100)</td>
<td>1/1 (100)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>V210I</td>
<td>1/1 (100)</td>
<td>1/1 (100)</td>
<td>not done</td>
</tr>
<tr>
<td>M232R</td>
<td>46/61 (75)</td>
<td>55/60 (92)</td>
<td>31/43 (72)</td>
</tr>
<tr>
<td>V180I+M232R</td>
<td>0/4 (0)</td>
<td>4/4 (100)</td>
<td>0/1 (0)</td>
</tr>
</tbody>
</table>

EE = glutamic acid homozygosity; EK = glutamic acid/lysine heterozygosity; KK = lysine homozygosity; MM = methionine homozygosity; MV = methionine/valine heterozygosity; PSWCs = periodic synchronous wave complexes
Table S11. Phenotypes of individuals with N-terminal PrP truncating variants

<table>
<thead>
<tr>
<th>HGVS</th>
<th>Variant</th>
<th>Zygosity</th>
<th>Sex</th>
<th>Age</th>
<th>Available phenotype information</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.59_60insC</td>
<td>G20Gfs84X</td>
<td>Het</td>
<td>F</td>
<td>79</td>
<td>Ascertained as part of the Rotterdam Study (89), a prospective cohort study of middle-aged and elderly persons. In good health and free of dementia as of at least age 78, at last in-person examination completion. Has 5 siblings and 2 children. Only family history noted is that one sibling has had a stroke before age 65.</td>
</tr>
<tr>
<td>c.109C&gt;T</td>
<td>R37X</td>
<td>Het</td>
<td>M</td>
<td>73</td>
<td>Ascertained as a control for the Swedish schizophrenia study. Underwent heart bypass surgery in 2008, has a family history of heart problems. 4 siblings. Reports no family history of neurodegeneration or neuropathy.</td>
</tr>
<tr>
<td>c.223C&gt;T</td>
<td>Q75X</td>
<td>Het</td>
<td>M</td>
<td>52</td>
<td>Ascertained in a study of type 2 diabetes. Has mild type 2 diabetes treated with metformin. Has children.</td>
</tr>
<tr>
<td>c.391G&gt;T</td>
<td>G131X</td>
<td>Het</td>
<td>F</td>
<td></td>
<td>None available.</td>
</tr>
</tbody>
</table>
Figure S1. Age of ExAC individuals with reportedly pathogenic PRNP variants versus all individuals in ExAC.

The distribution of ages, available for 40 of 52 individuals with reportedly pathogenic PRNP variants, did not differ from the distribution overall (p = .69, Wilcoxon rank-sum test; p = .69, student's t test) nor after controlling for cohort (p = .15, linear regression).
Figure S2. Sanger sequencing results for individuals with N-terminal truncating variants

Figure S2A. G20Gfs84X
Reverse (top) and forward (bottom).
Primers: 2a-forward: AACTTAGGGTCACATTTGTCTTTG; 2a-reverse: GGTAACGCTGATGTTCAGG; 2b forward: GTGGTGTCAGGTCAGG; 2b reverse: TTTCCAGTGCTCATCGTGC.
**Figure S2B. R37X**

DNA from whole blood (top) and fibroblasts (bottom).

Primers: PrP2-F: TGGGACTCTGACGTTCTCCT; PrP2-R: GGTGAAGTTCTCCCCCTTGG

**Figure S2C. Q75X.**

Supplementary references


