SUPPLEMENTAL INFORMATION

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

Table of Contents

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 ($p = 1 \times 10^{-12}$, 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.

Country	Australia	France	Germany	Italy	Japan	Netherlands	Spain	U.K.	U.S.	TOTAL
Start year	1993	1991	1993	1993	1999	1993	1993	1990	2000	
End year	2014	2013	2015	2013	2014	2013	2013	2013	2014	
Definite plus probable cases	553	2383	2690	1684	2144	409	1280	1963	2919	16025
Of which PRNP sequenced	152	1774	1307	1054	1533	163	749	1088	2640	10460
Proportion sequenced	27%	74%	49%	63%	72%	40%	59%	55%	90%	65%
Cumulative allele count of rare variants	31	196	125	396	464	22	127	173	361	1895
2-OPRD						3				3
1-OPRI		2	1						4	7
2-OPRI							1		5	6
3-OPRI		1	1							2
4-OPRI		1	3				2	13	4	23
5-OPRI		2	10			1	1	13	12	39
6-OPRI		2						35	15	52
7-OPRI		1	1			1		2		5
8-OPRI		10								10
9-OPRI									4	4
10-OPRI								1		1
OPRI (length				9	8					17

unspecified)										
A2V			1							1
G54S								1	4	5
P84S								1		1
G88A							1			1
G94S									1	1
H96Y							1			1
P102L	2	10	7	59	83		1	34	25	221
P105L					12			1		13
P105S									1	1
P105T	3		2							5
G114V									1	1
A117V		3				8	1	12	9	33
G131V						1				1
S132I								1		1
A133V	1								1	2
R148H			1						2	3
Q160X									1	1
Y163X								2		2
D167G								1		1
V176G	1									1
D178N	3	34	32	18	5	4	65	12	36	209
V180I		1		1	218				5	225
T183A									3	3
Q186X									1	1
H187A									1	1
H187R									7	7
T188A	1									1

T188K			2						1	3
T188R									12	12
E196A									1	1
E196K		3	8	2						13
F198S									5	5
E200G									1	1
E200K	11	101	28	123	63	2	52	38	153	571
V203I		5		3	4*				5	17
R208H		1	2	7	1				4	15
V210I	4	13	19	171	1			3	36	247
E211Q		5	2	3				1		11
E211D		1								1
Q212P								2		2
I215V							1			1
Y218N							1			1
A224V									1	1
Y226X						1				1
Q227X						1				1
M232R					63					63
V180I *trans* M232R					4					4
Variant not specified	5		5		2					12

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

Variant	First report	See also
P39L	Bernardi 2014 *(23)*	
2-OPRD	Beck 2001 *(24)*	Capellari 2002 *(25)*
1-OPRI	Laplanche 1995 *(26)*	Pietrini 2003 *(27)*
2-OPRI	Hill 2006 *(28)*	
3-OPRI	Nishida 2004 *(29)*	
4-OPRI	Laplanche 1995 *(26)*	Campbell 1996 *(30)*, Kaski 2011 *(31)*
5-OPRI	Goldfarb 1991 *(32)*	
6-OPRI	Owen 1990 *(33)*	Mead 2006 *(34)*
7-OPRI	Goldfarb 1991 *(32)*	Lewis 2003 *(35)*
8-OPRI	Goldfarb 1991 *(32)*	Laplanche 1999 *(36)*
9-OPRI	Krasemann 1995 *(37)*	
12-OPRI	Kumar 2011 *(38)*	
P84S	Jones 2014 *(39)*	
S97N	Zheng 2008 *(40)*	
P102L	Goldgaber 1989 *(41)*	Hsiao 1989 *(42)*
P105L	Yamada 1993 *(43)*	Yamada 1999 *(44)*
P105S	Tunnell 2008 *(45)*	
P105T	Polymenidou 2011*(46)*	
G114V	Rodriguez 2005 *(47)*	Liu 2010 *(48)*
A117V	Tateishi 1990 *(49)*	Hsiao 1991 *(50)*
129insLGGLGGYV	Hinnell 2011 *(51)*	
G131V	Panegyres 2001 *(52)*	Jansen 2012 *(53)*
S132I	Hilton 2009 *(54)*	
A133V	Rowe 2007 *(55)*	
Y145X	Kitamoto 1993 *(56)*	
R148H	Krebs 2005 *(1)*	Pastore 2005 *(2)*
Q160X	Finckh 2000 *(57)*	Jayadev 2011 *(58)*

Y163X	Revesz 2009 *(59)*	Mead 2013 *(60)*
D167G	Bishop 2009 *(61)*	
D167N	Beck 2010 *(22)*	
V176G	Simpson 2013 *(62)*	
D178Efs25X	Mastuzono 2013 *(63)*	
D178N	Goldfarb 1991 *(64)*	Medori 1992 *(65)*, Goldfarb 1992 *(66)*
V180I	Hitoshi 1993 *(67)*	Chasseigneaux 2006 *(68)*
T183A	Nitrini 1997 *(17)*	Grasbon-Frodl 2004 *(69)*
H187R	Butefisch 2000 *(70)*	
T188A	Collins 2000 *(71)*	
T188K	Finckh 2000 *(57)*	Roeber 2008 *(4)*
T188R	Windl 1999 *(3)*	Roeber 2008 *(4)*, Tartaglia 2010 *(5)*
T193I	Kotta 2006 *(72)*	
E196A	Zhang 2014 *(73)*	
E196K	Peoc'h 2000 *(6)*	
F198S	Farlow 1989 *(74)*	Hsiao 1992 *(18)*
F198V	Zheng 2008 *(40)*	
E200G	Kim 2013 *(75)*	
E200K	Goldgaber 1989 *(41)*	Hsiao 1991 *(76)*
D202G	Heinemann 2008 *(77)*	
D202N	Piccardo 1998 *(78)*	
V203I	Peoc'h 2000 *(6)*	
R208C	Zheng 2008 *(40)*	
R208H	Mastrianni 1996 *(79)*	Capellari 2005 *(11)*, Roeber 2005 *(12)*
V210I	Ripoll 1993 *(80)*	Pocchiari 1993 *(81)*, Mouillet-Richard 1999 *(82)*
E211D	Peoc'h 2012 *(83)*	
E211Q	Peoc'h 2000 *(6)*	
Q212P	Piccardo 1998 *(78)*	
I215V	Munoz-Nieto 2013 *(84)*	
Q217R	Hsiao 1992 *(18)*	
Y218N	Alzualde 2010 *(85)*	

Y226X	Jansen 2010 *(86)*	
Q227X	Jansen 2010 *(86)*	
M232R	Hitoshi 1993 *(67)*	Hoque 1996 *(87)*
M232T	Bratosiewicz 2000 *(88)*	
P238S	Windl 1999 *(3)*	

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.

Chrom	Pos	Ref	Alt	HGVS	Variant	Class	Call rate	AC
20	4679863	C	T	c.-4C>T		non-coding	97%	1
20	4679871	C	T	c.5C>T	A2V	missense	97%	2
20	4679877	T	A	c.11T>A	L4H	missense	98%	3
20	4679877	T	G	c.11T>G	L4R	missense	98%	1
20	4679888	A	G	c.22A>G	M8V	missense	98%	1
20	4679901	T	C	c.35T>C	F12S	missense	98%	1
20	4679916	G	C	c.50G>C	S17T	missense	98%	10
20	4679920	C	A	c.54C>A	D18E	missense	98%	2
20	4679920	C	T	c.54C>T	D18D	synonymous	98%	18
20	4679927	C	A	c.61C>A	L21I	missense	98%	1
20	4679932	C	T	c.66C>T	C22C	synonymous	98%	2
20	4679935	G	A	c.69G>A	K23K	synonymous	98%	2
20	4679939	C	T	c.73C>T	R25C	missense	98%	2
20	4679944	G	A	c.78G>A	P26P	synonymous	98%	6
20	4679967	G	T	c.101G>T	G34V	missense	98%	1
20	4679969	G	A	c.103G>A	G35S	missense	98%	1

20	4679975	C	T	c.109C>T	R37X	nonsense	98%	1
20	4679982	C	T	c.116C>T	P39L	missense	98%	3
20	4679983	G	A	c.117G>A	P39P	synonymous	98%	8
20	4679986	G	A	c.120G>A	G40G	synonymous	98%	12
20	4680005	A	G	c.139A>G	N47D	missense	98%	1
20	4680026	G	A	c.160G>A	G54S	missense	97%	78
20	4680028	T	C	c.162T>C	G54G	synonymous	97%	5
20	4680038	G	T	c.172G>T	G58W	missense	97%	1
20	4680045	C	T	c.179C>T	P60L	missense	96%	1
20	4680055	T	A	c.189T>A	G63G	synonymous	96%	1
20	4680077	G	A	c.211G>A	G71S	missense	96%	1
20	4680089	C	T	c.223C>T	Q75X	nonsense	96%	1
20	4680091	G	A	c.225G>A	Q75Q	synonymous	96%	2
20	4680093	C	G	c.227C>G	P76R	missense	96%	1
20	4680129	G	C	c.263G>C	G88A	missense	98%	1
20	4680134	G	A	c.268G>A	G90S	missense	98%	1
20	4680145	T	G	c.279T>G	G93G	synonymous	99%	1
20	4680151	C	T	c.285C>T	T95T	synonymous	99%	1
20	4680172	G	A	c.306G>A	P102P	synonymous	99%	21
20	4680185	A	G	c.319A>G	T107A	missense	99%	1
20	4680199	C	T	c.333C>T	H111H	synonymous	99%	2
20	4680202	G	A	c.336G>A	M112I	missense	99%	1
20	4680231	T	G	c.365T>G	V122G	missense	99%	1
20	4680232	G	T	c.366G>T	V122V	synonymous	99%	3
20	4680244	C	A	c.378C>A	G126G	synonymous	99%	1
20	4680244	C	T	c.378C>T	G126G	synonymous	99%	3
20	4680250	C	T	c.384C>T	Y128Y	synonymous	100%	22
20	4680252	T	C	c.386T>C	M129T	missense	100%	1

20	4680257	G	T	c.391G>T	G131X	nonsense	100%	1
20	4680258	G	T	c.392G>T	G131V	missense	100%	1
20	4680259	A	G	c.393A>G	G131G	synonymous	100%	3
20	4680262	T	C	c.396T>C	S132S	synonymous	100%	1
20	4680274	G	A	c.408G>A	R136R	synonymous	100%	2
20	4680274	G	T	c.408G>T	R136S	missense	100%	2
20	4680279	T	C	c.413T>C	I138T	missense	100%	1
20	4680289	C	T	c.423C>T	F141F	synonymous	100%	2
20	4680292	C	T	c.426C>T	G142G	synonymous	100%	1
20	4680299	T	G	c.433T>G	Y145D	missense	100%	1
20	4680308	C	T	c.442C>T	R148C	missense	100%	1
20	4680309	G	A	c.443G>A	R148H	missense	100%	3
20	4680311	T	C	c.445T>C	Y149H	missense	100%	1
20	4680316	T	C	c.450T>C	Y150Y	synonymous	100%	1
20	4680317	C	T	c.451C>T	R151C	missense	100%	2
20	4680318	G	A	c.452G>A	R151H	missense	100%	3
20	4680324	A	G	c.458A>G	N153S	missense	100%	1
20	4680328	G	A	c.462G>A	M154I	missense	100%	1
20	4680342	A	G	c.476A>G	N159S	missense	100%	1
20	4680349	G	A	c.483G>A	V161V	synonymous	100%	1
20	4680359	C	T	c.493C>T	P165S	missense	100%	2
20	4680362	A	G	c.496A>G	M166V	missense	100%	2
20	4680364	G	A	c.498G>A	M166I	missense	100%	2
20	4680373	C	T	c.507C>T	Y169Y	synonymous	100%	1
20	4680382	G	A	c.516G>A	Q172Q	synonymous	100%	1
20	4680385	C	T	c.519C>T	N173N	synonymous	100%	5
20	4680394	G	A	c.528G>A	V176V	synonymous	100%	2
20	4680397	C	G	c.531C>G	H177Q	missense	100%	1

20	4680397	C	T	c.531C>T	H177H	synonymous	100%	4
20	4680403	C	T	c.537C>T	C179C	synonymous	100%	1
20	4680404	G	A	c.538G>A	V180I	missense	100%	6
20	4680412	C	G	c.546C>G	I182M	missense	100%	2
20	4680429	C	G	c.563C>G	T188R	missense	100%	3
20	4680429	C	T	c.563C>T	T188M	missense	100%	4
20	4680443	A	G	c.577A>G	T193A	missense	100%	2
20	4680445	C	A	c.579C>A	T193T	synonymous	100%	1
20	4680449	G	C	c.583G>C	G195R	missense	100%	3
20	4680451	G	A	c.585G>A	G195G	synonymous	100%	3
20	4680453	A	C	c.587A>C	E196A	missense	100%	9
20	4680462	C	A	c.596C>A	T199N	missense	100%	1
20	4680463	C	T	c.597C>T	T199T	synonymous	100%	2
20	4680467	A	T	c.601A>T	T201S	missense	100%	1
20	4680469	C	T	c.603C>T	T201T	synonymous	100%	3
20	4680470	G	A	c.604G>A	D202N	missense	100%	1
20	4680472	C	T	c.606C>T	D202D	synonymous	100%	8
20	4680473	G	A	c.607G>A	V203I	missense	100%	3
20	4680488	C	T	c.622C>T	R208C	missense	100%	1
20	4680489	G	A	c.623G>A	R208H	missense	100%	9
20	4680490	C	T	c.624C>T	R208R	synonymous	100%	4
20	4680491	G	A	c.625G>A	V209M	missense	100%	1
20	4680494	G	A	c.628G>A	V210I	missense	100%	2
20	4680501	A	C	c.635A>C	Q212P	missense	100%	1
20	4680502	G	A	c.636G>A	Q212Q	synonymous	100%	2
20	4680520	C	T	c.654C>T	Y218Y	synonymous	100%	17
20	4680534	A	T	c.668A>T	Q223L	missense	100%	1
20	4680539	T	C	c.673T>C	Y225H	missense	99%	1

20	4680540	A	G	c.674A>G	Y225C	missense	99%	1
20	4680541	T	C	c.675T>C	Y225Y	synonymous	99%	3
20	4680552	G	A	c.686G>A	G229E	missense	98%	1
20	4680553	A	G	c.687A>G	G229G	synonymous	98%	1
20	4680561	T	G	c.695T>G	M232R	missense	97%	10
20	4680566	C	T	c.700C>T	L234F	missense	95%	29
20	4680590	C	T	c.724C>T	L242F	missense	87%	1
20	4680598	C	G	c.732C>G	I244M	missense	84%	1
20	4680598	C	T	c.732C>T	I244I	synonymous	84%	1
20	4680626	T	G	c.760T>G	X254G	read-through	66%	1

Table S4. Summary of rare *PRNP* variants by functional class in ExAC

Class	Total AC
missense	236
non-coding	1
nonsense	3
read-through	1
synonymous	180

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.

Variant	dbSNP id	23andMe id	Called genotypes	AC	Comments
P102L	rs74315401	i5004359	502075	1-5	

A117V	rs74315402	i5004358	501820	total	
D178N	rs74315403	i5004357	502450		
E200K	rs28933385	rs28933385	531370		
M232R	rs74315409	i5004352	502475	78	AC=29 in 2,685 individuals with >90% Japanese ancestry
V180I	rs74315408	i5004353	502125	15	AC=1-5 in 2,670 individuals with >90% Japanese ancestry
V210I	rs74315407	i5004354	502290	13	AC=8 in 385,030 Europeans
R208C	rs55826236	rs55826236	501850	8	
R208H	rs74315412	i5004349	501775	22	AC=19 in 384,645 Europeans
P105L	rs11538758	rs11538758	531575	1-5 total	
G131V	rs74315410	i5004351	499455		
A133V	rs74315415	i5004347	502520		
T183A	rs74315411	i5004350	502295		
F198V	rs55871421	rs55871421	501540		
F198S	rs74315405	i5004356	502460		
G217R	rs74315406	i5004355	502385		

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.

Cohort phenotype	**Total in ExAC**	**Number with reportedly pathogenic *PRNP* variants**
Autoimmune	1675	4
Cancer	7601	3
Cardiovascular	14622	14
Metabolic	15327	19
Mixed	3936	2
Population controls	2215	6
Psychiatric	15330	4
Total	**60706**	**52**

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.

Variant	**Populations**	**Codon 129 genotypes**
P39L	1 PJL, 2 TSI	2 M/M, 1 M/V
G131V	1 TSI	1 M/V
R148H	1 CEU, 1 IBS, 1 PJL	3 M/M
V180I	1 CHB, 2 JPT, 3 PJL	4 M/M, 1 M/V, 1 V/V
T188R	1 CLM, 2 MXL	1 M/V, 2 V/V

E196A	3 CHB, 6 CHS	9 M/M
D202N	1 TSI	1 M/V
V203I	1 IBS, 2 TSI	1 M/M, 2 M/V
R208C	1 ACB	1 M/M
R208H	1 ACB, 2 ASW, 1 CLM, 2 IBS, 1 MSL, 2 TSI	4 M/M, 5 M/V
V210I	2 TSI	2 M/M
Q212P	1 CEU	1 M/V
M232R	5 CHB, 5 JPT	10 M/M

Table S8. Inferred ancestry of all ExAC individuals.

Methods for ancestry assignment are described in Materials and Methods.

Population code	Description	Super population	N in ExAC
ACB	African Caribbeans in Barbados	AFR	2267
ASW	Americans of African Ancestry in SW USA	AFR	2151
BEB	Bengali from Bangladesh	SAS	483
CDX	Chinese Dai in Xishuangbanna, China	EAS	19
CEU	Utah Residents (CEPH) with Northern and Western European ancestry	EUR	14185
CHB	Han Chinese in Beijing, China	EAS	1553
CHS	Southern Han Chinese	EAS	1733
CLM	Colombians from Medellin, Colombia	AMR	870
ESN	Esan in Nigeria	AFR	89
FIN	Finnish in Finland	EUR	3977
GBR	British in England and Scotland	EUR	10358
GIH	Gujarati Indian from Houston, Texas	SAS	79
GWD	Gambian in Western Divisions in The Gambia	AFR	102
IBS	Iberian population in Spain	EUR	3534

ITU	Indian Telugu from the UK	SAS	1089
JPT	Japanese in Tokyo, Japan	EAS	663
KHV	Kinh in Ho Chi Minh City, Vietnam	EAS	369
LWK	Luhya in Webuye, Kenya	AFR	72
MSL	Mende in Sierra Leone	AFR	189
MXL	Mexican Ancestry from Los Angeles USA	AMR	2658
PEL	Peruvians from Lima, Peru	AMR	1900
PJL	Punjabi from Lahore, Pakistan	SAS	6300
PUR	Puerto Ricans from Puerto Rico	AMR	579
STU	Sri Lankan Tamil from the UK	SAS	460
TSI	Toscani in Italia	EUR	4795
YRI	Yoruba in Ibadan, Nigeria	AFR	232

Table S9. Inferred ancestry of 23andMe research participants

Ancestry	**Minimum called genotypes**	**Maximum called genotypes**	**Total allele count of reportedly pathogenic *PRNP* variants**
European	382865	408475	≥35
Latino	42425	44480	≥10
African	22945	23795	≥10
East Asian	20255	21710	≥75
All others	30975	33125	≥20
TOTAL	499455	531575	141

Table S10. Details of Japanese prion disease cases

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

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

Variant	Duration**	(range)	Codon 129	Codon 219
Insertion	27.8 ± 17.7	(3-57)	MM 6; MV 1	EE 6; KK 1
P102L	48.4 ± 35.8	(2-186)	MM 67; MV 6	EE 70; EK 2
P105L	90.2 ± 40.4	(25-184)	MV 11	EE 7
D178N-129M	8.5 ± 4.4	(2-13)	MM 4	EE 4
D178N-129V	24		MV 1	EE 1
V180I	16.4 ± 14.5	(0-70)	MM 162; MV 54	EE 210
E200K	5.0 ± 6.0	(1-32)	MM 58; MV 3	EE 58; EK 3
V203I	3.7 ± 2.1	(1-6)	MM 3	EE 3

R208H	3		MM 1	EE 1
V210I	3		MM 1	EE 1
M232R	8.6 ± 12.7	(0-78)	MM 60; MV 2	EE 61; EK 1
V180I+M232R	21.8 ± 17.7	(1-47)	MM 4	EE 4

182 **Duration between the onset and akinetic mutism or death without akinetic mutism. Duration is
183 expressed as the mean ± SD (range) months.
184

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

185 EE = glutamic acid homozygosity; EK = glutamic acid/lysine heterozygosity; KK = lysine
186 homozygosity; MM = methionine homozygosity; MV = methionine/valine heterozygosity; PSWCs
187 = periodic synchronous wave complexes
188
189
190

Table S11. Phenotypes of individuals with N-terminal PrP truncating variants

HGVS	Variant	Zygosity	Sex	Age	Available phenotype information
c.59_60insC	G20Gfs84X	Het	F	79	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.
c.109C>T	R37X	Het	M	73	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.
c.223C>T	Q75X	Het	M	52	Ascertained in a study of type 2 diabetes. Has mild type 2 diabetes treated with metformin. Has children.
c.391G>T	G131X	Het	F		None available.

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).

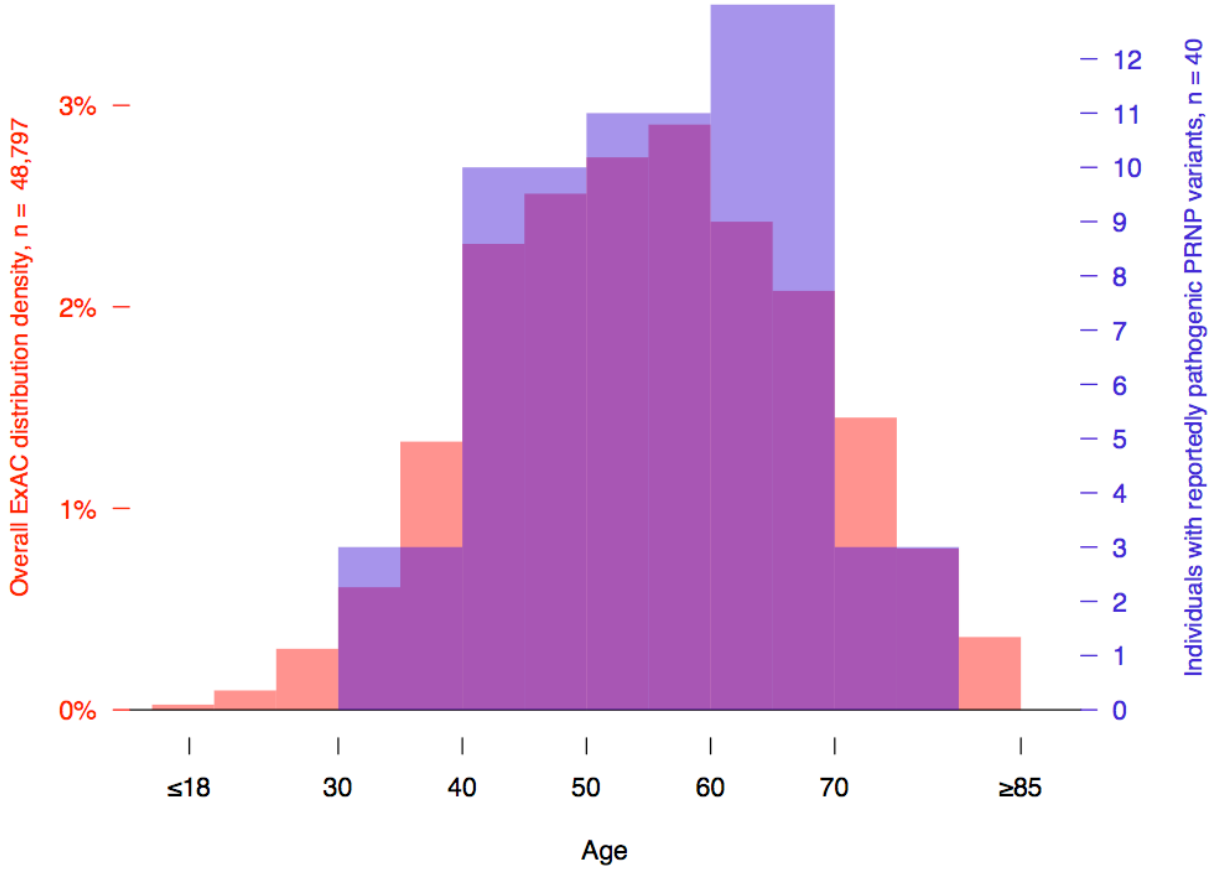


Figure S2. Sanger sequencing results for individuals with N-terminal truncating variants

Figure S2A. G20Gfs84X

Reverse (top) and forward (bottom).

Primers: 2a-forward: AACTTAGGGTCACATTTGTCCTTGG; 2a-reverse: GGTAACGGTGCATGTTTTCACG. 2b forward: GTGGTGGCTGGGGTCAAGG; 2b reverse: TTTCCAGTGCCCATCAGTGC.

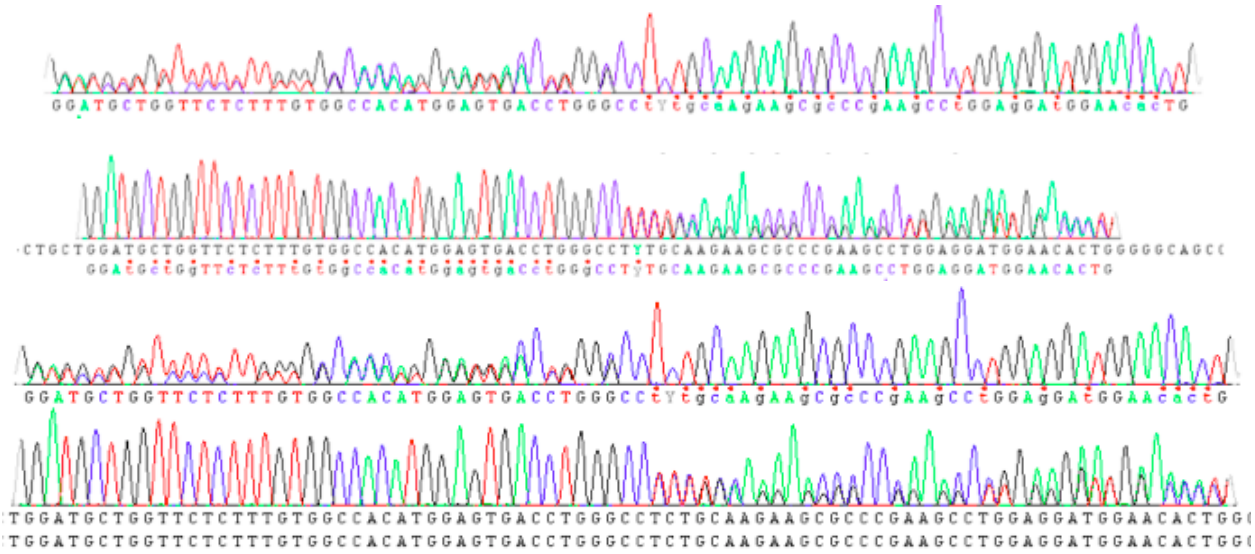


Figure S2B. R37X

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

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

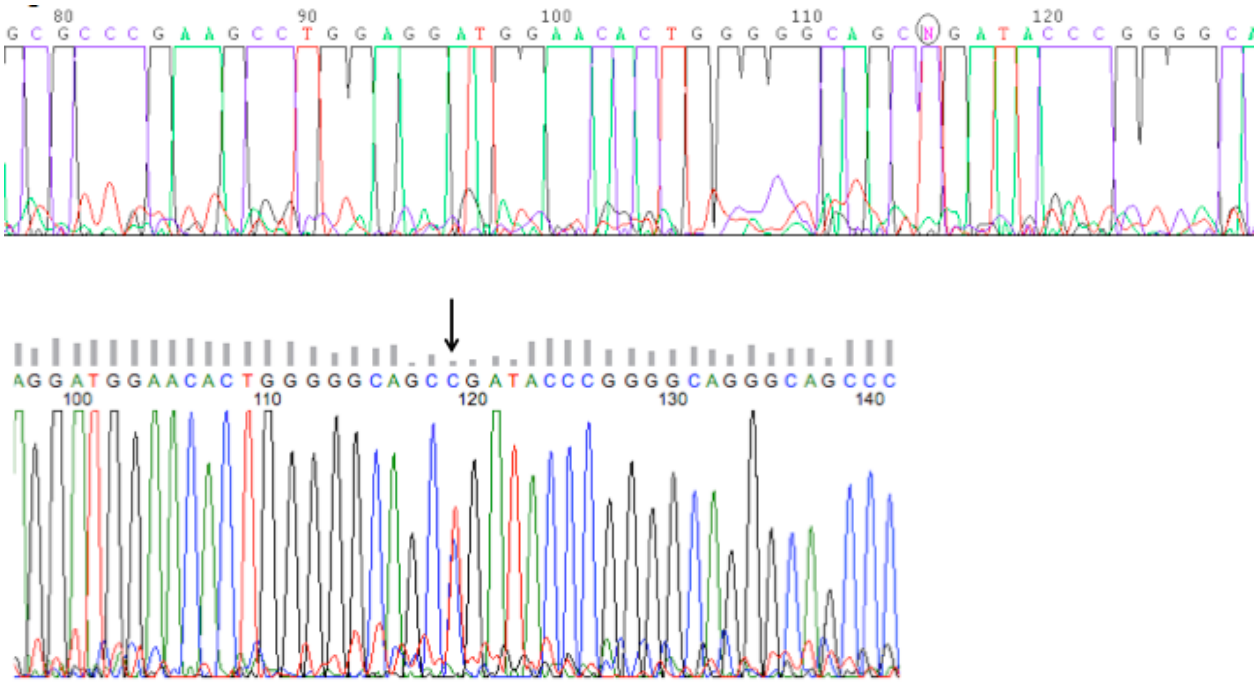
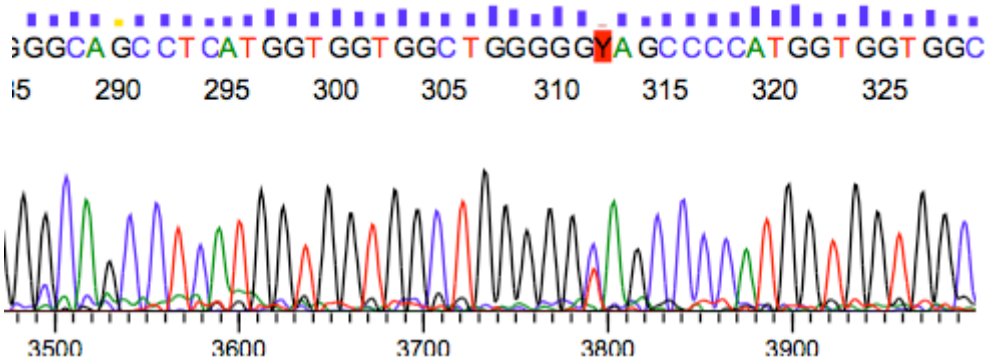


Figure S2C. Q75X.

Primers: PRNP_EX2-M13-F [TGTAAAACGACGGCCAGT] CCATTGCTATGCACTCATTCA;

PRNP_EX2-M13-R [CAGGAAACAGCTATGACC] CCATGTGCTTCATGTTGGTT



Supplementary references

1. B. Krebs, R.-M. Lederer, O. Windl, E.-M. Grasbon-Frodl, I. Zerr, H. A. Kretzschmar, Creutzfeldt-Jakob disease associated with an R148H mutation of the prion protein gene, *Neurogenetics* **6**, 97–100 (2005).

2. M. Pastore, S. S. Chin, K. L. Bell, Z. Dong, Q. Yang, L. Yang, J. Yuan, S. G. Chen, P. Gambetti, W.-Q. Zou, Creutzfeldt-Jakob disease (CJD) with a mutation at codon 148 of prion protein gene: relationship with sporadic CJD, *Am. J. Pathol.* **167**, 1729–1738 (2005).

3. O. Windl, A. Giese, W. Schulz-Schaeffer, I. Zerr, K. Skworc, S. Arendt, C. Oberdieck, M. Bodemer, S. Poser, H. A. Kretzschmar, Molecular genetics of human prion diseases in Germany, *Hum. Genet.* **105**, 244–252 (1999).

4. S. Roeber, E.-M. Grasbon-Frodl, O. Windl, B. Krebs, W. Xiang, C. Vollmert, T. Illig, A. Schröter, T. Arzberger, P. Weber, I. Zerr, H. A. Kretzschmar, Evidence for a pathogenic role of different mutations at codon 188 of PRNP, *PloS One* **3**, e2147 (2008).

5. M. C. Tartaglia, J. N. Thai, T. See, A. Kuo, R. Harbaugh, B. Raudabaugh, I. Cali, M. Sattavat, H. Sanchez, S. J. DeArmond, M. D. Geschwind, Pathologic evidence that the T188R mutation in PRNP is associated with prion disease, *J. Neuropathol. Exp. Neurol.* **69**, 1220–1227 (2010).

6. K. Peoc'h, P. Manivet, P. Beaudry, F. Attane, G. Besson, D. Hannequin, N. Delasnerie-Lauprêtre, J. L. Laplanche, Identification of three novel mutations (E196K, V203I, E211Q) in the prion protein gene (PRNP) in inherited prion diseases with Creutzfeldt-Jakob disease phenotype, *Hum. Mutat.* **15**, 482 (2000).

7. B.-H. Jeong, Y.-C. Jeon, Y.-J. Lee, H.-J. Cho, S.-J. Park, D.-I. Chung, J. Kim, S. H. Kim, H.-T. Kim, E.-K. Choi, K.-C. Choi, R. I. Carp, Y.-S. Kim, Creutzfeldt-Jakob disease with the V203I mutation and M129V polymorphism of the prion protein gene (PRNP) and a 17 kDa prion protein fragment, *Neuropathol. Appl. Neurobiol.* **36**, 558–563 (2010).

8. Q. Shi, C. Chen, X.-J. Wang, W. Zhou, J.-C. Wang, B.-Y. Zhang, C. Gao, C. Gao, J. Han, X.-P. Dong, Rare V203I mutation in the PRNP gene of a Chinese patient with Creutzfeldt-Jakob disease, *Prion* **7**, 259–262 (2013).

9. J. Komatsu, K. Sakai, T. Hamaguchi, Y. Sugiyama, K. Iwasa, M. Yamada, Creutzfeldt-Jakob disease associated with a V203I homozygous mutation in the prion protein gene, *Prion* **8**, 336–338 (2014).

10. J. A. Mastrianni, C. Iannicola, R. M. Myers, S. DeArmond, S. B. Prusiner, Mutation of the prion protein gene at codon 208 in familial Creutzfeldt-Jakob disease, *Neurology* **47**, 1305–1312 (1996).

11. S. Capellari, F. Cardone, S. Notari, M. E. Schininà, B. Maras, D. Sità, A. Baruzzi, M. Pocchiari, P. Parchi, Creutzfeldt-Jakob disease associated with the R208H mutation in the prion protein gene, *Neurology* **64**, 905–907 (2005).

12. S. Roeber, B. Krebs, M. Neumann, O. Windl, I. Zerr, E.-M. Grasbon-Frodl, H. A. Kretzschmar, Creutzfeldt-Jakob disease in a patient with an R208H mutation of the prion protein gene (PRNP) and a 17-kDa prion protein fragment, *Acta Neuropathol. (Berl.)* **109**, 443–448 (2005).

13. C. Basset-Leobon, E. Uro-Coste, K. Peoc'h, S. Haik, V. Sazdovitch, M. Rigal, O. Andreoletti, J.-J. Hauw, M.-B. Delisle, Familial Creutzfeldt-Jakob disease with an R208H-129V haplotype and Kuru plaques, *Arch. Neurol.* **63**, 449–452 (2006).

14. C. Chen, Q. Shi, C. Tian, Q. Li, W. Zhou, C. Gao, J. Han, X.-P. Dong, The first Chinese case of Creutzfeldt-Jakob disease patient with R208H mutation in PRNP, *Prion* **5**, 232–234 (2011).

15. R. Matěj, G. G. Kovacs, S. Johanidesová, J. Keller, M. Matějčková, J. Nováková, V. Sigut, O. Keller, R. Rusina, Genetic Creutzfeldt-Jakob disease with R208H mutation presenting as progressive supranuclear palsy, *Mov. Disord. Off. J. Mov. Disord. Soc.* **27**, 476–479 (2012).

16. M. G. Vita, S. Gaudino, D. Di Giuda, D. Sauchelli, P. E. Alboini, E. Gangemi, A. Bizzarro, E. Scaricamazza, S. Capellari, P. Parchi, C. Masullo, R208H-129VV haplotype in the prion protein gene: phenotype and neuroimaging of a patient with genetic Creutzfeldt-Jakob disease, *J. Neurol.* **260**, 2650–2652 (2013).

17. R. Nitrini, S. Rosemberg, M. R. Passos-Bueno, L. S. da Silva, P. Iughetti, M. Papadopoulos, P. M. Carrilho, P. Caramelli, S. Albrecht, M. Zatz, A. LeBlanc, Familial spongiform encephalopathy associated with a novel prion protein gene mutation, *Ann. Neurol.* **42**, 138–146 (1997).

18. K. Hsiao, S. R. Dlouhy, M. R. Farlow, C. Cass, M. Da Costa, P. M. Conneally, M. E. Hodes, B. Ghetti, S. B. Prusiner, Mutant prion proteins in Gerstmann-Sträussler-Scheinker disease with neurofibrillary tangles, *Nat. Genet.* **1**, 68–71 (1992).

19. D. G. MacArthur, T. A. Manolio, D. P. Dimmock, H. L. Rehm, J. Shendure, G. R. Abecasis, D. R. Adams, R. B. Altman, S. E. Antonarakis, E. A. Ashley, J. C. Barrett, L. G. Biesecker, D. F. Conrad, G. M. Cooper, N. J. Cox, M. J. Daly, M. B. Gerstein, D. B. Goldstein, J. N. Hirschhorn, S. M. Leal, L. A. Pennacchio, J. A. Stamatoyannopoulos, S. R. Sunyaev, D. Valle, B. F. Voight, W. Winckler, C. Gunter, Guidelines for investigating causality of sequence variants in human disease, *Nature* **508**, 469–476 (2014).

20. S. Richards, N. Aziz, S. Bale, D. Bick, S. Das, J. Gastier-Foster, W. W. Grody, M. Hegde, E. Lyon, E. Spector, K. Voelkerding, H. L. Rehm, ACMG Laboratory Quality Assurance Committee, Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical

Genetics and Genomics and the Association for Molecular Pathology, *Genet. Med. Off. J. Am. Coll. Med. Genet.* **17**, 405–424 (2015).

21. E. S. Simon, E. Kahana, J. Chapman, T. A. Treves, R. Gabizon, H. Rosenmann, N. Zilber, A. D. Korczyn, Creutzfeldt-Jakob disease profile in patients homozygous for the PRNP E200K mutation, *Ann. Neurol.* **47**, 257–260 (2000).

22. J. A. Beck, M. Poulter, T. A. Campbell, G. Adamson, J. B. Uphill, R. Guerreiro, G. S. Jackson, J. C. Stevens, H. Manji, J. Collinge, S. Mead, PRNP allelic series from 19 years of prion protein gene sequencing at the MRC Prion Unit, *Hum. Mutat.* **31**, E1551–1563 (2010).

23. L. Bernardi, C. Cupidi, F. Frangipane, M. Anfossi, M. Gallo, M. E. Conidi, F. Vasso, R. Colao, G. Puccio, S. A. M. Curcio, M. Mirabelli, A. Clodomiro, R. Di Lorenzo, N. Smirne, R. Maletta, A. C. Bruni, Novel N-terminal domain mutation in prion protein detected in 2 patients diagnosed with frontotemporal lobar degeneration syndrome, *Neurobiol. Aging* **35**, 2657.e7–11 (2014).

24. J. A. Beck, S. Mead, T. A. Campbell, A. Dickinson, D. P. Wientjens, E. A. Croes, C. M. Van Duijn, J. Collinge, Two-octapeptide repeat deletion of prion protein associated with rapidly progressive dementia, *Neurology* **57**, 354–356 (2001).

25. S. Capellari, P. Parchi, B. D. Wolff, J. Campbell, R. Atkinson, D. M. Posey, R. B. Petersen, P. Gambetti, Creutzfeldt-Jakob disease associated with a deletion of two repeats in the prion protein gene, *Neurology* **59**, 1628–1630 (2002).

26. J. L. Laplanche, N. Delasnerie-Lauprêtre, J. P. Brandel, M. Dussaucy, J. Chatelain, J. M. Launay, Two novel insertions in the prion protein gene in patients with late-onset dementia, *Hum. Mol. Genet.* **4**, 1109–1111 (1995).

27. V. Pietrini, G. Puoti, L. Limido, G. Rossi, G. Di Fede, G. Giaccone, M. Mangieri, F. Tedeschi, A. Bondavalli, D. Mancia, O. Bugiani, F. Tagliavini, Creutzfeldt-Jakob disease with a novel extra-repeat insertional mutation in the PRNP gene, *Neurology* **61**, 1288–1291 (2003).

28. A. F. Hill, S. Joiner, J. A. Beck, T. A. Campbell, A. Dickinson, M. Poulter, J. D. F. Wadsworth, J. Collinge, Distinct glycoform ratios of protease resistant prion protein associated with PRNP point mutations, *Brain J. Neurol.* **129**, 676–685 (2006).

29. Y. Nishida, N. Sodeyama, Y. Toru, S. Toru, T. Kitamoto, H. Mizusawa, Creutzfeldt-Jakob disease with a novel insertion and codon 219 Lys/Lys polymorphism in PRNP, *Neurology* **63**, 1978–1979 (2004).

30. T. A. Campbell, M. S. Palmer, R. G. Will, W. R. Gibb, P. J. Luthert, J. Collinge, A prion disease with a novel 96-base pair insertional mutation in the prion protein gene, *Neurology* **46**, 761–766 (1996).

343 31. D. N. Kaski, C. Pennington, J. Beck, M. Poulter, J. Uphill, M. T. Bishop, J. M.
344 Linehan, C. O'Malley, J. D. F. Wadsworth, S. Joiner, R. S. G. Knight, J. W. Ironside, S.
345 Brandner, J. Collinge, S. Mead, Inherited prion disease with 4-octapeptide repeat
346 insertion: disease requires the interaction of multiple genetic risk factors, *Brain J.*
347 *Neurol.* **134**, 1829–1838 (2011).

348 32. L. G. Goldfarb, P. Brown, W. R. McCombie, D. Goldgaber, G. D. Swergold, P. R.
349 Wills, L. Cervenakova, H. Baron, C. J. Gibbs, D. C. Gajdusek, Transmissible familial
350 Creutzfeldt-Jakob disease associated with five, seven, and eight extra octapeptide
351 coding repeats in the PRNP gene, *Proc. Natl. Acad. Sci. U. S. A.* **88**, 10926–10930
352 (1991).

353 33. F. Owen, M. Poulter, T. Shah, J. Collinge, R. Lofthouse, H. Baker, R. Ridley, J.
354 McVey, T. J. Crow, An in-frame insertion in the prion protein gene in familial Creutzfeldt-
355 Jakob disease, *Brain Res. Mol. Brain Res.* **7**, 273–276 (1990).

356 34. S. Mead, M. Poulter, J. Beck, T. E. F. Webb, T. A. Campbell, J. M. Linehan, M.
357 Desbruslais, S. Joiner, J. D. F. Wadsworth, A. King, P. Lantos, J. Collinge, Inherited
358 prion disease with six octapeptide repeat insertional mutation--molecular analysis of
359 phenotypic heterogeneity, *Brain J. Neurol.* **129**, 2297–2317 (2006).

360 35. V. Lewis, S. Collins, A. F. Hill, A. Boyd, C. A. McLean, M. Smith, C. L. Masters,
361 Novel prion protein insert mutation associated with prolonged neurodegenerative
362 illness, *Neurology* **60**, 1620–1624 (2003).

363 36. J. L. Laplanche, K. H. Hachimi, I. Durieux, P. Thuillet, L. Defebvre, N. Delasnerie-
364 Lauprêtre, K. Peoc'h, J. F. Foncin, A. Destée, Prominent psychiatric features and early
365 onset in an inherited prion disease with a new insertional mutation in the prion protein
366 gene, *Brain J. Neurol.* **122 (Pt 12)**, 2375–2386 (1999).

367 37. S. Krasemann, I. Zerr, T. Weber, S. Poser, H. Kretzschmar, G. Hunsmann, W.
368 Bodemer, Prion disease associated with a novel nine octapeptide repeat insertion in the
369 PRNP gene, *Brain Res. Mol. Brain Res.* **34**, 173–176 (1995).

370 38. N. Kumar, B. F. Boeve, B. P. Boot, C. F. Orr, J. Duffy, B. K. Woodruff, A. K. Nair, J.
371 Ellison, K. Kuntz, K. Kantarci, C. R. Jack, B. F. Westmoreland, J. A. Fields, M. Baker, R.
372 Rademakers, J. E. Parisi, D. W. Dickson, Clinical characterization of a kindred with a
373 novel 12-octapeptide repeat insertion in the prion protein gene, *Arch. Neurol.* **68**, 1165–
374 1170 (2011).

375 39. M. Jones, S. Odunsi, D. du Plessis, A. Vincent, M. Bishop, M. W. Head, J. W.
376 Ironside, D. Gow, Gerstmann-Straüssler-Scheinker disease: novel PRNP mutation and
377 VGKC-complex antibodies, *Neurology* **82**, 2107–2111 (2014).

378 40. L. Zheng, J. Longfei, Y. Jing, Z. Xinqing, S. Haiqing, L. Haiyan, W. Fen, D. Xiumin,
379 J. Jianping, PRNP mutations in a series of apparently sporadic neurodegenerative
380 dementias in China, *Am. J. Med. Genet. Part B Neuropsychiatr. Genet. Off. Publ. Int.*
381 *Soc. Psychiatr. Genet.* **147B**, 938–944 (2008).

382 41. D. Goldgaber, L. G. Goldfarb, P. Brown, D. M. Asher, W. T. Brown, S. Lin, J. W.
383 Teener, S. M. Feinstone, R. Rubenstein, R. J. Kascsak, Mutations in familial
384 Creutzfeldt-Jakob disease and Gerstmann-Sträussler-Scheinker's syndrome, *Exp.*
385 *Neurol.* **106**, 204–206 (1989).

386 42. K. Hsiao, H. F. Baker, T. J. Crow, M. Poulter, F. Owen, J. D. Terwilliger, D.
387 Westaway, J. Ott, S. B. Prusiner, Linkage of a prion protein missense variant to
388 Gerstmann-Sträussler syndrome, *Nature* **338**, 342–345 (1989).

389 43. M. Yamada, Y. Itoh, H. Fujigasaki, S. Naruse, K. Kaneko, T. Kitamoto, J. Tateishi,
390 E. Otomo, M. Hayakawa, J. Tanaka, A missense mutation at codon 105 with codon 129
391 polymorphism of the prion protein gene in a new variant of Gerstmann-Sträussler-
392 Scheinker disease, *Neurology* **43**, 2723–2724 (1993).

393 44. M. Yamada, Y. Itoh, A. Inaba, Y. Wada, M. Takashima, S. Satoh, T. Kamata, R.
394 Okeda, T. Kayano, N. Suematsu, T. Kitamoto, E. Otomo, M. Matsushita, H. Mizusawa,
395 An inherited prion disease with a PrP P105L mutation: clinicopathologic and PrP
396 heterogeneity, *Neurology* **53**, 181–188 (1999).

397 45. E. Tunnell, R. Wollman, S. Mallik, C. J. Cortes, S. J. Dearmond, J. A. Mastrianni, A
398 novel PRNP-P105S mutation associated with atypical prion disease and a rare PrPSc
399 conformation, *Neurology* **71**, 1431–1438 (2008).

400 46. M. Polymenidou, S. Prokop, H. H. Jung, E. Hewer, D. Peretz, R. Moos, M. Tolnay,
401 A. Aguzzi, Atypical prion protein conformation in familial prion disease with PRNP
402 P105T mutation, *Brain Pathol. Zurich Switz.* **21**, 209–214 (2011).

403 47. M.-M. Rodriguez, K. Peoc'h, S. Haïk, C. Bouchet, L. Vernengo, G. Mañana, R.
404 Salamano, L. Carrasco, M. Lenne, P. Beaudry, J.-M. Launay, J.-L. Laplanche, A novel
405 mutation (G114V) in the prion protein gene in a family with inherited prion disease,
406 *Neurology* **64**, 1455–1457 (2005).

407 48. Z. Liu, L. Jia, Y. Piao, D. Lu, F. Wang, H. Lv, Y. Lu, J. Jia, Creutzfeldt-Jakob disease
408 with PRNP G114V mutation in a Chinese family, *Acta Neurol. Scand.* **121**, 377–383
409 (2010).

410 49. J. Tateishi, T. Kitamoto, K. Doh-ura, Y. Sakaki, G. Steinmetz, C. Tranchant, J. M.
411 Warter, N. Heldt, Immunochemical, molecular genetic, and transmission studies on a
412 case of Gerstmann-Sträussler-Scheinker syndrome, *Neurology* **40**, 1578–1581 (1990).

413 50. K. K. Hsiao, C. Cass, G. D. Schellenberg, T. Bird, E. Devine-Gage, H. Wisniewski,
414 S. B. Prusiner, A prion protein variant in a family with the telencephalic form of
415 Gerstmann-Sträussler-Scheinker syndrome, *Neurology* **41**, 681–684 (1991).

416 51. C. Hinnell, M. B. Coulthart, G. H. Jansen, N. R. Cashman, J. Lauzon, A. Clark, F.
417 Costello, C. White, R. Midha, S. Wiebe, S. Furtado, Gerstmann-Straussler-Scheinker
418 disease due to a novel prion protein gene mutation, *Neurology* **76**, 485–487 (2011).

52. P. K. Panegyres, K. Toufexis, B. A. Kakulas, L. Cernevakova, P. Brown, B. Ghetti, P. Piccardo, S. R. Dlouhy, A new PRNP mutation (G131V) associated with Gerstmann-Sträussler-Scheinker disease, *Arch. Neurol.* **58**, 1899–1902 (2001).

53. C. Jansen, P. Parchi, S. Capellari, C. A. Ibrahim-Verbaas, M. Schuur, R. Strammiello, P. Corrado, M. T. Bishop, W. A. van Gool, M. M. Verbeek, F. Baas, W. van Saane, W. G. M. Spliet, G. H. Jansen, C. M. van Duijn, A. J. M. Rozemuller, Human prion diseases in the Netherlands (1998-2009): clinical, genetic and molecular aspects, *PloS One* **7**, e36333 (2012).

54. D. A. Hilton, M. W. Head, V. K. Singh, M. Bishop, J. W. Ironside, Familial prion disease with a novel serine to isoleucine mutation at codon 132 of prion protein gene (PRNP), *Neuropathol. Appl. Neurobiol.* **35**, 111–115 (2009).

55. D. B. Rowe, V. Lewis, M. Needham, M. Rodriguez, A. Boyd, C. McLean, H. Roberts, C. L. Masters, S. J. Collins, Novel prion protein gene mutation presenting with subacute PSP-like syndrome, *Neurology* **68**, 868–870 (2007).

56. T. Kitamoto, R. Iizuka, J. Tateishi, An amber mutation of prion protein in Gerstmann-Sträussler syndrome with mutant PrP plaques, *Biochem. Biophys. Res. Commun.* **192**, 525–531 (1993).

57. U. Finckh, T. Müller-Thomsen, U. Mann, C. Eggers, J. Marksteiner, W. Meins, G. Binetti, A. Alberici, C. Hock, R. M. Nitsch, A. Gal, High prevalence of pathogenic mutations in patients with early-onset dementia detected by sequence analyses of four different genes, *Am. J. Hum. Genet.* **66**, 110–117 (2000).

58. S. Jayadev, D. Nochlin, P. Poorkaj, E. J. Steinbart, J. A. Mastrianni, T. J. Montine, B. Ghetti, G. D. Schellenberg, T. D. Bird, J. B. Leverenz, Familial prion disease with Alzheimer disease-like tau pathology and clinical phenotype, *Ann. Neurol.* **69**, 712–720 (2011).

59. T. Revesz, J. L. Holton, T. Lashley, G. Plant, B. Frangione, A. Rostagno, J. Ghiso, Genetics and molecular pathogenesis of sporadic and hereditary cerebral amyloid angiopathies, *Acta Neuropathol. (Berl.)* **118**, 115–130 (2009).

60. S. Mead, S. Gandhi, J. Beck, D. Caine, D. Gajulapalli, D. Gallujipali, C. Carswell, H. Hyare, S. Joiner, H. Ayling, T. Lashley, J. M. Linehan, H. Al-Doujaily, B. Sharps, T. Revesz, M. K. Sandberg, M. M. Reilly, M. Koltzenburg, A. Forbes, P. Rudge, S. Brandner, J. D. Warren, J. D. F. Wadsworth, N. W. Wood, J. L. Holton, J. Collinge, A novel prion disease associated with diarrhea and autonomic neuropathy, *N. Engl. J. Med.* **369**, 1904–1914 (2013).

61. M. T. Bishop, C. Pennington, C. A. Heath, R. G. Will, R. S. G. Knight, PRNP variation in UK sporadic and variant Creutzfeldt Jakob disease highlights genetic risk factors and a novel non-synonymous polymorphism, *BMC Med. Genet.* **10**, 146 (2009).

62. M. Simpson, V. Johanssen, A. Boyd, G. Klug, C. L. Masters, Q.-X. Li, R. Pamphlett, C. McLean, V. Lewis, S. J. Collins, Unusual clinical and molecular-pathological profile of gerstmann-Sträussler-Scheinker disease associated with a novel PRNP mutation (V176G), *JAMA Neurol.* **70**, 1180–1185 (2013).

63. K. Matsuzono, Y. Ikeda, W. Liu, T. Kurata, S. Deguchi, K. Deguchi, K. Abe, A novel familial prion disease causing pan-autonomic-sensory neuropathy and cognitive impairment, *Eur. J. Neurol. Off. J. Eur. Fed. Neurol. Soc.* **20**, e67–69 (2013).

64. L. G. Goldfarb, M. Haltia, P. Brown, A. Nieto, J. Kovanen, W. R. McCombie, S. Trapp, D. C. Gajdusek, New mutation in scrapie amyloid precursor gene (at codon 178) in Finnish Creutzfeldt-Jakob kindred, *Lancet* **337**, 425 (1991).

65. R. Medori, H. J. Tritschler, A. LeBlanc, F. Villare, V. Manetto, H. Y. Chen, R. Xue, S. Leal, P. Montagna, P. Cortelli, Fatal familial insomnia, a prion disease with a mutation at codon 178 of the prion protein gene, *N. Engl. J. Med.* **326**, 444–449 (1992).

66. L. G. Goldfarb, R. B. Petersen, M. Tabaton, P. Brown, A. C. LeBlanc, P. Montagna, P. Cortelli, J. Julien, C. Vital, W. W. Pendelbury, Fatal familial insomnia and familial Creutzfeldt-Jakob disease: disease phenotype determined by a DNA polymorphism, *Science* **258**, 806–808 (1992).

67. S. Hitoshi, H. Nagura, H. Yamanouchi, T. Kitamoto, Double mutations at codon 180 and codon 232 of the PRNP gene in an apparently sporadic case of Creutzfeldt-Jakob disease, *J. Neurol. Sci.* **120**, 208–212 (1993).

68. S. Chasseigneaux, S. Haïk, I. Laffont-Proust, O. De Marco, M. Lenne, J.-P. Brandel, J.-J. Hauw, J.-L. Laplanche, K. Peoc'h, V180I mutation of the prion protein gene associated with atypical PrPSc glycosylation, *Neurosci. Lett.* **408**, 165–169 (2006).

69. E. Grasbon-Frodl, H. Lorenz, U. Mann, R. M. Nitsch, O. Windl, H. A. Kretzschmar, Loss of glycosylation associated with the T183A mutation in human prion disease, *Acta Neuropathol. (Berl.)* **108**, 476–484 (2004).

70. C. M. Bütefisch, P. Gambetti, L. Cervenakova, K. Y. Park, M. Hallett, L. G. Goldfarb, Inherited prion encephalopathy associated with the novel PRNP H187R mutation: a clinical study, *Neurology* **55**, 517–522 (2000).

71. S. Collins, A. Boyd, A. Fletcher, K. Byron, C. Harper, C. A. McLean, C. L. Masters, Novel prion protein gene mutation in an octogenarian with Creutzfeldt-Jakob disease, *Arch. Neurol.* **57**, 1058–1063 (2000).

72. K. Kotta, I. Paspaltsis, S. Bostantjopoulou, H. Latsoudis, A. Plaitakis, D. Kazis, J. Collinge, T. Sklaviadis, Novel mutation of the PRNP gene of a clinical CJD case, *BMC Infect. Dis.* **6**, 169 (2006).

73. H. Zhang, M. Wang, L. Wu, H. Zhang, T. Jin, J. Wu, L. Sun, Novel prion protein gene mutation at codon 196 (E196A) in a septuagenarian with Creutzfeldt-Jakob disease, *J. Clin. Neurosci. Off. J. Neurosurg. Soc. Australas.* **21**, 175–178 (2014).

74. M. R. Farlow, R. D. Yee, S. R. Dlouhy, P. M. Conneally, B. Azzarelli, B. Ghetti, Gerstmann-Sträussler-Scheinker disease. I. Extending the clinical spectrum, *Neurology* **39**, 1446–1452 (1989).

75. M.-O. Kim, I. Cali, A. Oehler, J. C. Fong, K. Wong, T. See, J. S. Katz, P. Gambetti, B. M. Bettcher, S. J. Dearmond, M. D. Geschwind, Genetic CJD with a novel E200G mutation in the prion protein gene and comparison with E200K mutation cases, *Acta Neuropathol. Commun.* **1**, 80 (2013).

76. K. Hsiao, Z. Meiner, E. Kahana, C. Cass, I. Kahana, D. Avrahami, G. Scarlato, O. Abramsky, S. B. Prusiner, R. Gabizon, Mutation of the prion protein in Libyan Jews with Creutzfeldt-Jakob disease, *N. Engl. J. Med.* **324**, 1091–1097 (1991).

77. U. Heinemann, A. Krasnianski, B. Meissner, E. M. Grasbon-Frodl, H. A. Kretzschmar, I. Zerr, Novel PRNP mutation in a patient with a slow progressive dementia syndrome, *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.* **14**, CS41–43 (2008).

78. P. Piccardo, S. R. Dlouhy, P. M. Lievens, K. Young, T. D. Bird, D. Nochlin, D. W. Dickson, H. V. Vinters, T. R. Zimmerman, I. R. Mackenzie, S. J. Kish, L. C. Ang, C. De Carli, M. Pocchiari, P. Brown, C. J. Gibbs, D. C. Gajdusek, O. Bugiani, J. Ironside, F. Tagliavini, B. Ghetti, Phenotypic variability of Gerstmann-Sträussler-Scheinker disease is associated with prion protein heterogeneity, *J. Neuropathol. Exp. Neurol.* **57**, 979–988 (1998).

79. J. A. Mastrianni, C. Iannicola, R. M. Myers, S. DeArmond, S. B. Prusiner, Mutation of the prion protein gene at codon 208 in familial Creutzfeldt-Jakob disease, *Neurology* **47**, 1305–1312 (1996).

80. L. Ripoll, J. L. Laplanche, M. Salzmann, A. Jouvet, B. Planques, M. Dussaucy, J. Chatelain, P. Beaudry, J. M. Launay, A new point mutation in the prion protein gene at codon 210 in Creutzfeldt-Jakob disease, *Neurology* **43**, 1934–1938 (1993).

81. M. Pocchiari, M. Salvatore, F. Cutruzzolá, M. Genuardi, C. T. Allocatelli, C. Masullo, G. Macchi, G. Alemá, S. Galgani, Y. G. Xi, A new point mutation of the prion protein gene in Creutzfeldt-Jakob disease, *Ann. Neurol.* **34**, 802–807 (1993).

82. S. Mouillet-Richard, C. Teil, M. Lenne, S. Hugon, O. Taleb, J. L. Laplanche, Mutation at codon 210 (V210I) of the prion protein gene in a North African patient with Creutzfeldt-Jakob disease, *J. Neurol. Sci.* **168**, 141–144 (1999).

83. K. Peoc'h, E. Levavasseur, E. Delmont, A. De Simone, I. Laffont-Proust, N. Privat, Y. Chebaro, C. Chapuis, P. Bedoucha, J.-P. Brandel, A. Laquerriere, J.-L. Kemeny, J.-J. Hauw, M. Borg, H. Rezaei, P. Derreumaux, J.-L. Laplanche, S. Haïk, Substitutions at residue 211 in the prion protein drive a switch between CJD and GSS syndrome, a new

mechanism governing inherited neurodegenerative disorders, *Hum. Mol. Genet.* **21**, 5417–5428 (2012).

84. M. Muñoz-Nieto, N. Ramonet, J. I. López-Gastón, N. Cuadrado-Corrales, O. Calero, M. Díaz-Hurtado, J. R. Ipiens, S. Ramón y Cajal, J. de Pedro-Cuesta, M. Calero, A novel mutation I215V in the PRNP gene associated with Creutzfeldt-Jakob and Alzheimer's diseases in three patients with divergent clinical phenotypes, *J. Neurol.* **260**, 77–84 (2013).

85. A. Alzualde, B. Indakoetxea, I. Ferrer, F. Moreno, M. Barandiaran, A. Gorostidi, A. Estanga, I. Ruiz, M. Calero, F. W. van Leeuwen, B. Atares, R. Juste, A. B. Rodriguez-Martínez, A. López de Munain, A novel PRNP Y218N mutation in Gerstmann-Sträussler-Scheinker disease with neurofibrillary degeneration, *J. Neuropathol. Exp. Neurol.* **69**, 789–800 (2010).

86. C. Jansen, P. Parchi, S. Capellari, A. J. Vermeij, P. Corrado, F. Baas, R. Strammiello, W. A. van Gool, J. C. van Swieten, A. J. M. Rozemuller, Prion protein amyloidosis with divergent phenotype associated with two novel nonsense mutations in PRNP, *Acta Neuropathol. (Berl.)* **119**, 189–197 (2010).

87. M. Z. Hoque, T. Kitamoto, H. Furukawa, T. Muramoto, J. Tateishi, Mutation in the prion protein gene at codon 232 in Japanese patients with Creutzfeldt-Jakob disease: a clinicopathological, immunohistochemical and transmission study, *Acta Neuropathol. (Berl.)* **92**, 441–446 (1996).

88. J. Bratosiewicz, M. Barcikowska, L. Cervenakowa, P. Brown, D. C. Gajdusek, P. P. Liberski, A new point mutation of the PRNP gene in Gerstmann-Sträussler-Scheinker case in Poland, *Folia Neuropathol. Assoc. Pol. Neuropathol. Med. Res. Cent. Pol. Acad. Sci.* **38**, 164–166 (2000).

89. A. Hofman, S. Darwish Murad, C. M. van Duijn, O. H. Franco, A. Goedegebure, M. A. Ikram, C. C. W. Klaver, T. E. C. Nijsten, R. P. Peeters, B. H. C. Stricker, H. W. Tiemeier, A. G. Uitterlinden, M. W. Vernooij, The Rotterdam Study: 2014 objectives and design update, *Eur. J. Epidemiol.* **28**, 889–926 (2013).