SUPPLEMENTARY FILES

PSMF1 variants cause a phenotypic spectrum from early-onset Parkinson's disease to perinatal lethality by disrupting mitochondrial pathways

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Supplementary File 1. Pathogenicity predictions and computational analysis of 14 *PSMF1* variants detected in the study cohort

A. PSMF1 non-splice variants

	Variant *PSMF1* (GRCh38/hg38) [NM_006814.5]	gnomAD v2.1.1/v3.1.2/v4.0.0 (het, hom, allele frequency)	CADD	PolyPhen2 HVAR	SIFT4G	PROVEAN	MutationTaster	HSF	GERP (Franklin Genoox)	GERP (UCSC)
V1	chr20:1164436:C>G c.724C>G p.(Arg242Gly)	v2.1.1: 7 het, 0 hom, *f* = 0.00002787 v3.1.2: not found v4.0.0: 5 het, 0 hom, *f* = 0.000003420	27.4	Possibly damaging (score: 0.997)	Damaging (0, 0, 0, 0)	Damaging (-6.3, -6.3, -6.3, -3.21)	Disease causing (prob: 0.999978910569413)	No significant impact on splicing signals	4.13	4.13
V3	chr20:1164436:C>T c.724C>T p.(Arg242Cys)	v2.1.1: 2 het, 0 hom, *f* = 0.000007964 v3.1.2: 3 het, 0 hom, *f* = 0.00001972 v4.0.0: 8 het, 0 hom, *f* = 0.000004956	31	Possibly damaging (score: 0.999)	Damaging (0, 0, 0, 0)	Damaging (-7.21, -7.21, -7.21, -4.01)	Disease causing (prob: 0.999999926286941)	Alteration of auxiliary sequences: Significant alteration of ESE / ESS motifs ratio (-5)	4.13	4.13
V4	chr20:1164437:G>A c.725G>A p.(Arg242His)	v2.1.1: 427 het, 0 hom, *f* = 0.001511 v3.1.2: 224 het, 0 hom, *f* = 0.001472 v4.0.0: 3454 het, 4 hom, *f* = 0.002140	32	Possibly damaging (0.858)	Damaging (0, 0, 0, 0)	Damaging, Damaging, Damaging, Neutral (-4.5, -4.5, -4.5, -2.22)	Disease causing (prob: 0.999993833789465)	No significant impact on splicing signals	5.11	5.11
V5	chr20:1125525:C>A c.157C>A p.(Leu53Met)	v2.1.1: not found v3.1.2: not found v4.0.0: not found	23.2	Possibly damaging (score: 0.967)	Tolerated (0.226, 0.226, 0.226, 0.226)	Neutral (-1.15, -1.25, -1.05, -1.15)	Disease causing (prob: 0.999846573719514)	No significant impact on splicing signals	4.93	4.93
V6	chr20:1164394:C>G c.682C>G p.(Leu228Val)	v2.1.1: not found v3.1.2: not found v4.0.0: not found	22.3	Possibly damaging (score: 0.967)	Tolerated (0.228, 0.481, 0.228)	Neutral (-0.33, -0.36, -0.33)	Disease causing (prob: 0.988685291987796)	No significant impact on splicing signals	6.07	6.07
V7	chr20:1164403:C>T c.691C>T p.(Arg231*)	v2.1.1: not found v3.1.2: not found v4.0.0: 4 het, 0 hom, *f* = 0.000002736	37	N/A	N/A	N/A	Disease causing (prob: 1)	Alteration of auxiliary sequences: Significant alteration of ESE / ESS motifs ratio (-3)	5.13	5.13
V11	chr20:1118774:A>T c.1A>T p.(0)	v2.1.1: 1 het, 0 hom, *f* = 0.000004074 v3.1.2: not found v4.0.0: 1 het, 0 hom, *f* = 6.866e-7	24.5	Possibly damaging (score: 0.970)	Tolerated/ Damaging (0.278, 0, 0.259, 0.278)	Neutral (-1.18, -1.14, -1.24, -1.18)	Disease causing (prob: 1)	Alteration of auxiliary sequences: Significant alteration of ESE / ESS motifs ratio (-6)	4.61	4.61
V12	chr20:1118872:CG>C c.101del p.(Gly34Valfs*47)	v2.1.1: not found v3.1.2: 1 het, 0 hom, *f* = 0.000006568 v4.0.0: 4 het, 0 hom, *f* = 0.000002478	N/A	N/A	N/A	N/A	Disease causing (prob: 1)	Alteration of auxiliary sequences: Significant alteration of ESE / ESS motifs ratio (-2) New Donor splice site: Activation of a cryptic Donor site. Potential alteration of splicing (HSF)	N/A	4.26

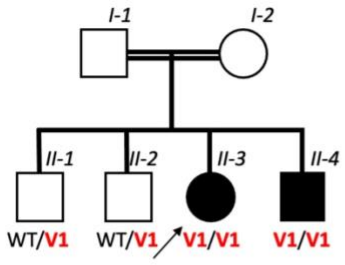
B. PSMF1 splice variants

	Variant *PSMF1* (GRCh38/hg38) [NM_006814.5]	gnomAD v2.1.1/v3.1.2/v4.0.0 (het, hom, allele frequency)	CADD	MutationTaster	HSF	SpliceSiteFinder-like [0-100]	MaxEntScan [0-12]	NNSPLICE [0-1]	GeneSplicer [0-24]	SpliceAI [≥0.2|0.5|0.8]	AbSplice [≥0.01|0.05|0.2]	GERP (Franklin Genoox)	GERP (UCSC)
V2	chr20:1125652:T>A c.282+2T>A	v2.1.1: 1 het, 0 hom, *f* = 0.000004052 v3.1.2: not found v4.0.0: not found	35	Disease causing (prob: 1)	Broken WT Donor Site: Alteration of the WT Donor site, most probably affecting splicing (site donor broken)	-100%	-100%	-100%	-100%	0.95 DG (15) 1.00 DL (-2)	0.33	4.93	4.93
V8	chr20:1125655:G>A c.282+5G>A	v2.1.1: 4 het, 0 hom, *f* = 0.00001448 v3.1.2: 1 het, 0 hom, *f* = 0.000006571 v4.0.0: 9 het, 0 hom, *f* = 0.000005597	29.3	Disease causing (prob: 1)	Broken WT Donor Site: Alteration of the WT Donor site, most probably affecting splicing (site donor broken)	-13.9%	-65.1%	-100%	-100%	0.89 DG (12) 0.96 DL (-5)	0.27	N/A	0.225
V9	chr20:1163184:G>A c.605+1G>A	v2.1.1: 5 het, 0 hom, *f* = 0.00001990 v3.1.2: 1 het, 0 hom, *f* = 0.000006570 v4.0.0: 23 het, 0 hom, *f* = 0.00001425	35	Disease causing (prob: 1)	Broken WT Donor Site: Alteration of the WT Donor site, most probably affecting splicing (site donor broken)	-100%	-100%	-100%	-100%	0.99 DL (-1)	0.36	5.36	5.36
V10	chr20:1164481:G>A c.764+5G>A	v2.1.1: 2 het, 0 hom, *f* = 0.000007979 v3.1.2: 2 het, 0 hom, *f* = 0.00001314 v4.0.0: 23 het, 0 hom, *f* = 0.000008055	24.4	Disease causing (prob: 1)	Broken WT Donor Site: Alteration of the WT Donor site, most probably affecting splicing (site donor broken)	-100%	-56.5%	-56.2%	-58.9%	0.34 DG (11) 0.78 DL (-5)	0.31	N/A	5.95
V13	chr20:1118904:T>C c.129+2T>C	v2.1.1: not found v3.1.2: not found v4.0.0: 8 het, 0 hom, *f* = 0.000005473	34	Disease causing (prob: 1)	Broken WT Donor Site: Alteration of the WT Donor site, most probably affecting splicing (site donor broken)	-2.5%	-100%	-100%	-100%	0.99 DL (-2)	0.14	3.96	3.96
V14	chr20:1127510:T>C c.365+2T>C	v2.1.1: not found v3.1.2: not found v4.0.0: 5 het, 0 hom, *f* = 0.000003505	33	Disease causing (prob: 1)	Broken WT Donor Site: Alteration of the WT Donor site, most probably affecting splicing (site donor broken)	0%	-100%	-100%	-100%	0.99 DL (-2)	0.22	4.53	4.53

Legend: CADD = Combined Annotation Dependent Depletion (https://cadd.gs.washington.edu/snv); ESE = Exonic Splicing Enhancer; ESS = Exonic Splicing Silencer; *f* = gnomAD allele frequency; GERP = Genomic Evolutionary Rate Profiling (http://mendel.stanford.edu/SidowLab/downloads/gerp/); GERP (UCSC) = Genomic Evolutionary Rate Profiling by University of California, Santa Cruz (https://genome.ucsc.edu/cgi-bin/hgTrackUi?db=hg19&g=allHg19RS_BW); gnomAD = The Genome Aggregation Database (https://gnomad.broadinstitute.org/); GRCh38/hg38 = Genome Reference Consortium Human Build 38 Organism: Homo sapiens (human); het = heterozygous entries; hom = homozygous entries; HSF = Human Splicing Finder (https://hsf.genomnis.com/home); MutationTaster = http://www.mutationtaster.org/; N/A = not applicable/not available; PolyPhen-2 HVAR: Polymorphism Phenotyping v2, HumVar model (http://genetics.bwh.harvard.edu/pph2/); Prob = probability; PROVEAN: Protein Variation Effect Analyzer (http://provean.jcvi.org/index.php); SIFT 4G: Sorting Intolerant From Tolerant Databases for Genome (https://sift.bii.a-star.edu.sg/sift4g/public//Homo_sapiens/); WT = wild type. V# indicates *PSMF1* variants (NM_006814.5) displayed with different font colors (Fig.1a-2a).

Supplementary File 2. Autozygosity mapping of probands carrying homozygous *PSMF1* variants and their relatives

Pedigree B

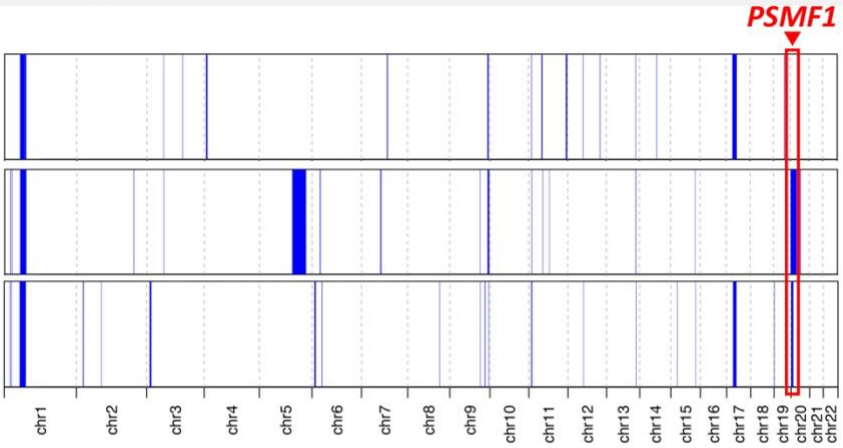


V1: 20:1,164,436C>G
c.724C>G p.(Arg242Gly)

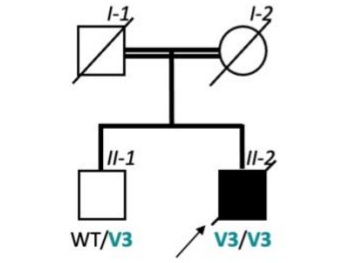
B-II-2
ROH = 67.76 Mb

B-II-3
ROH = 117.2 Mb
20:96,321-21,136,599

B-II-4
ROH = 75.01 Mb
20:96,321-7,779,697

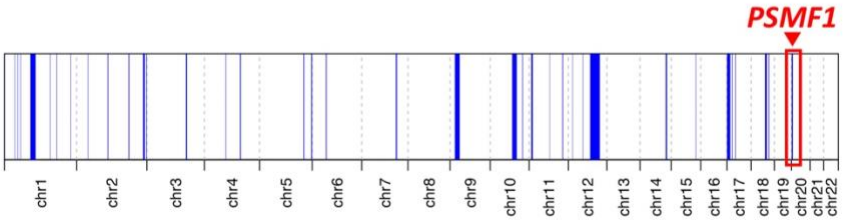


Pedigree C

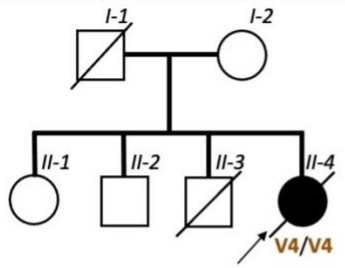


V3: 20:1,164,436C>T
c.724C>T p.(Arg242Cys)

C-II-2
ROH = 169.36 Mb
20:763,771-4,800,850

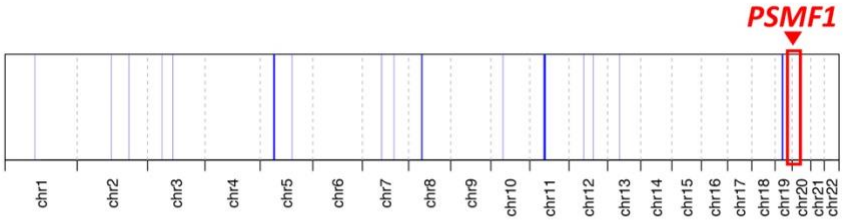


Pedigree D

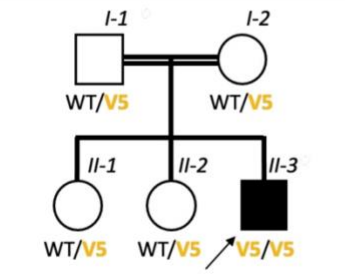


V4: 20:1,164,437G>A
c.725G>A p.(Arg242His)

D-II-4
ROH = 37.75 Mb

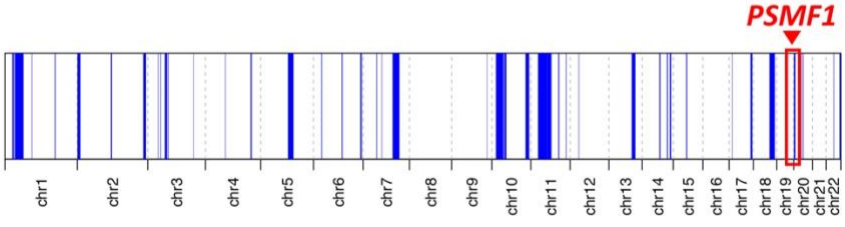


Pedigree E

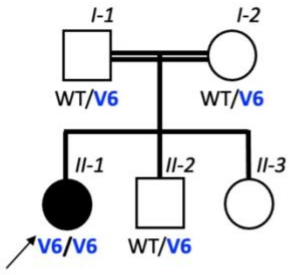


V5: 20:1,125,525C>A
c.157C>A p.(Leu53Met)

E-II-3
ROH = 309.82 Mb
20:483,858-5,501,992



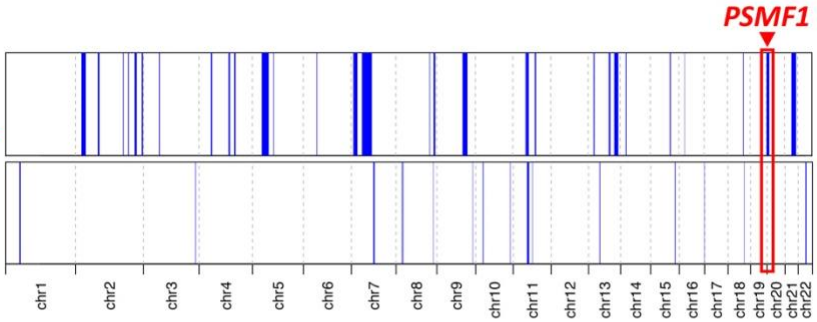
Pedigree F



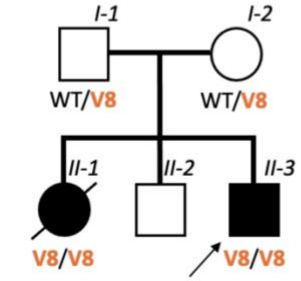
V6: 20:1,164,394C>G
c.682C>G p.(Leu228Val)

F-II-1
ROH = 234.53 Mb
20:96,321-10,038,445

F-II-2
ROH = 39.56 Mb

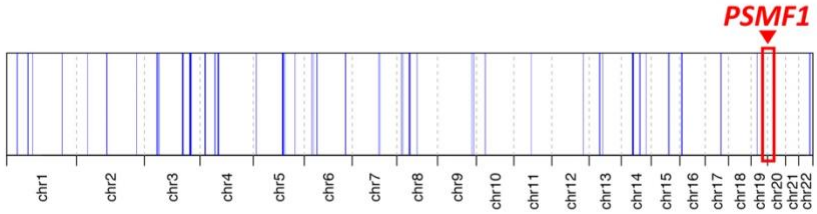


Pedigree H

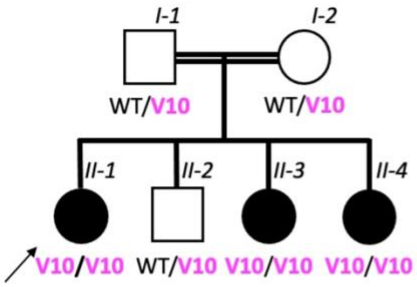


V8: 20:1,125,655G>A
c.282+5G>A

H-II-3
ROH = 106.13 Mb

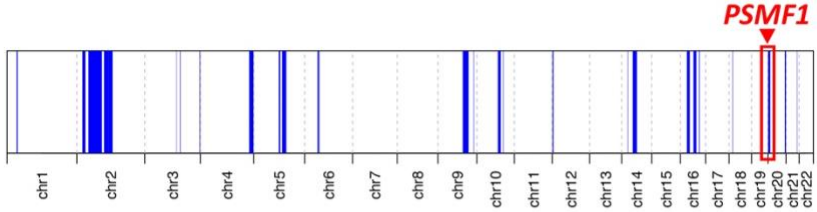


Pedigree J

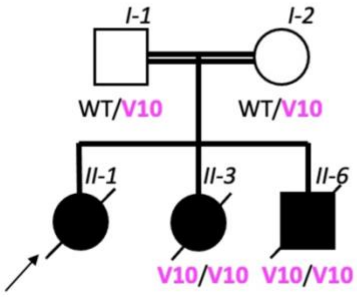


V10: 20:1,164,481G>A
c.764+5G>A

J-II-1
ROH = 227.47 Mb
20:96,321-7,779,059



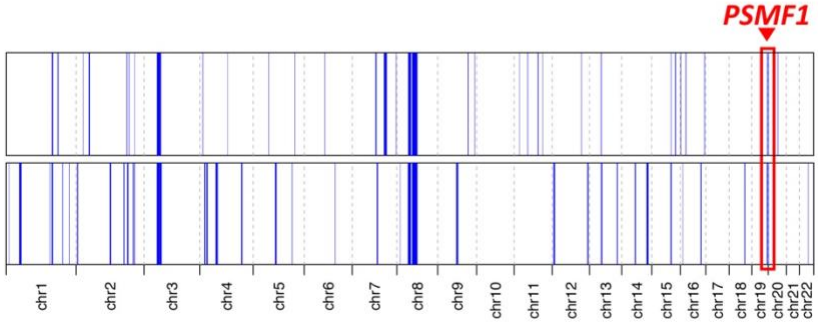
Pedigree K



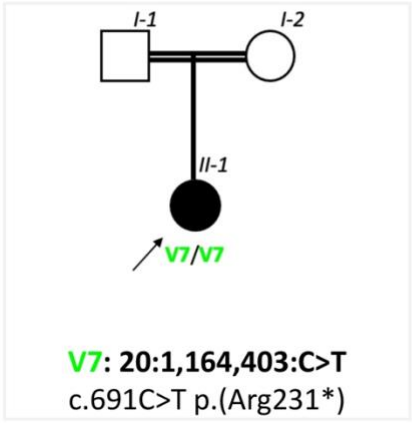
V10: 20:1,164,481G>A
c.764+5G>A

K-II-3
ROH = 111.18 Mb
20:96,321-1,927,653

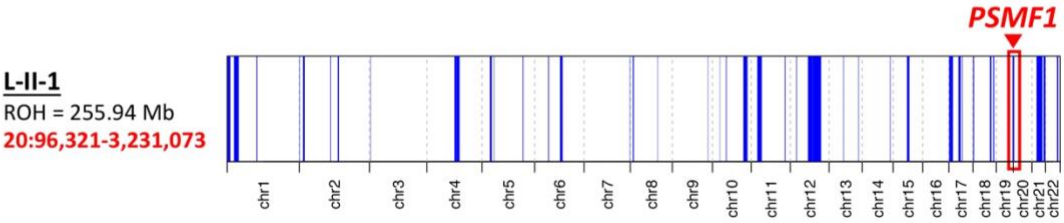
K-II-6
ROH = 167 Mb
20:96,321-1,927,734



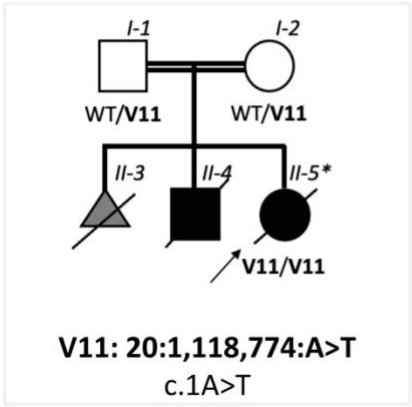
Pedigree L



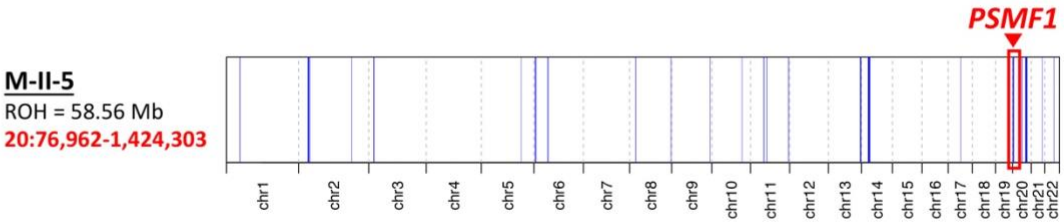
V7: 20:1,164,403:C>T
c.691C>T p.(Arg231*)



Pedigree M

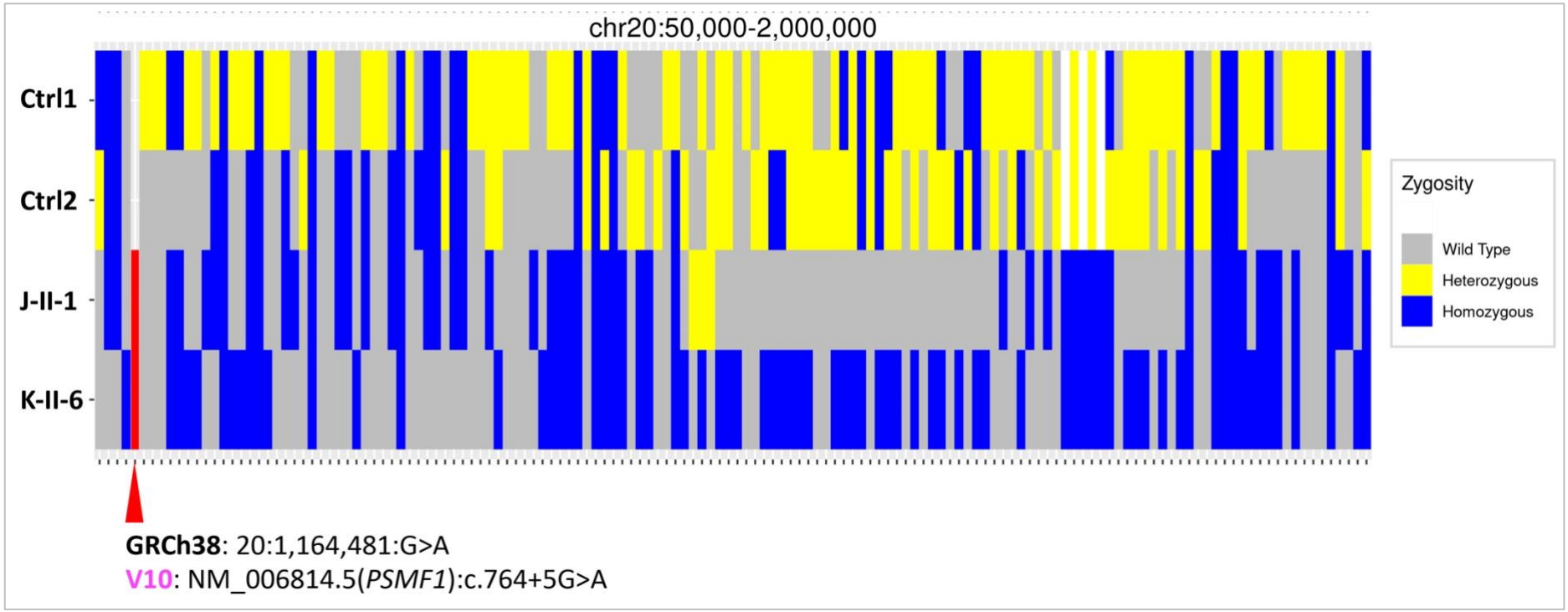


V11: 20:1,118,774:A>T
c.1A>T



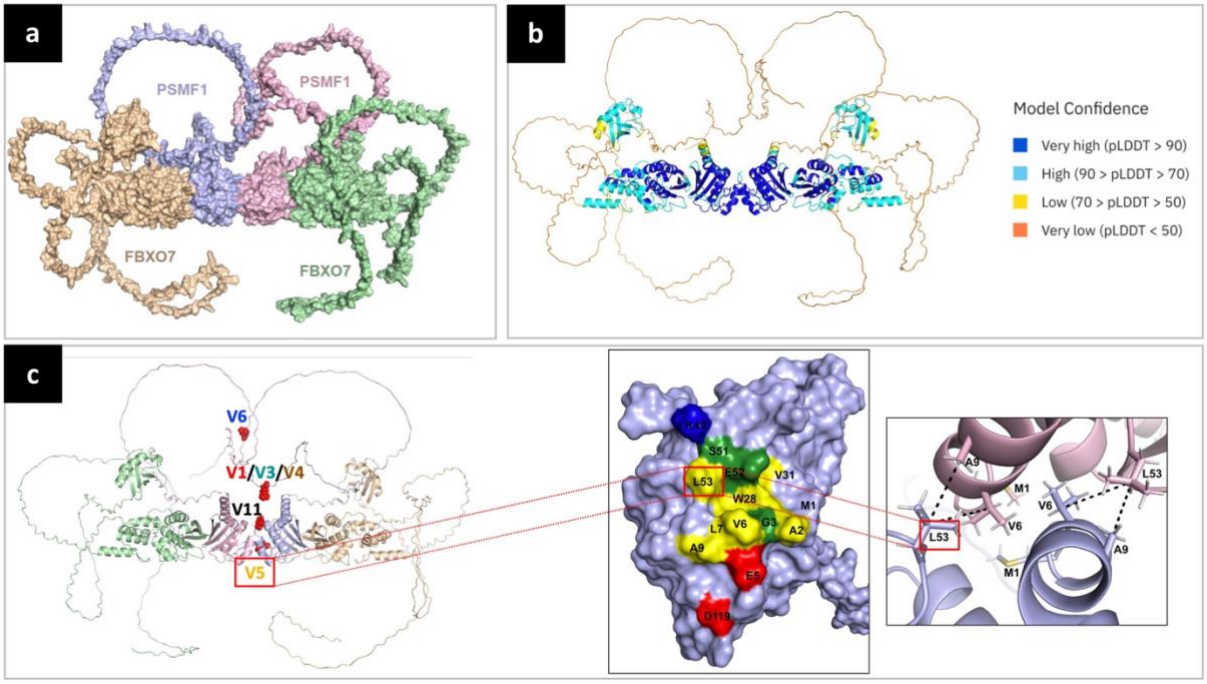
Legend: Autozygosity mapping using the tool AutoMap[1] identified regions of homozygosity (ROHs) larger than 2 Mb in all probands carrying homozygous *PSMF1* variants and their family members with raw data from exome or genome sequencing (VCF or FASTQ files) available. Proband of Pedigree I (I-II-3) was excluded from autozygosity mapping as raw data from exome sequencing were not traceable. Simplified pedigrees and genomic coordinates (GRCh38/hg38) of *PSMF1* variants segregating in the families are displayed on the left as a reference. V# indicates *PSMF1* variants referenced to *PSMF1* transcript NM_006814.5 and displayed with different font colors (see Fig. 1a-2a). Regions of homozygosity identified in single individuals are shown in blue, with their total genomic extension across autosomes (in Mb) reported in the middle part of each panel. ROHs containing *PSMF1* are marked with red boxes and arrowheads, with their genomic coordinates in single individuals displayed in red. GRCh38/hg38 = Genome Reference Consortium Human Build 38 Organism: Homo sapiens (human); Mb = megabase(s); ROH = region of homozygosity. **Fully identifying pedigrees are available upon request to the corresponding author.**

Supplementary File 3. Haplotype analysis of the splice variant NM_006814.5(*PSMF1*):c.764+5G>A found in the homozygous state in the proband of Pedigrees J-K



Legend: Haplotype analysis of the *PSMF1* splice variant NM_006814.5:c.764+5G>A which was detected in the homozygous state in the probands of Pedigrees J (J-II-1) and K (K-II-6; Fig.1a). Color banding identifies the *PSMF1* variant under investigation in red, homozygous variants in blue, heterozygous variants in yellow and wild-type bases in gray. Different pattern of variants flanking the above-mentioned *PSMF1* variant suggests that this mutational event is recurrent rather than inherited from a common ancestor. Genomic coordinates are based on the human reference genome assembly GRCh38/hg38. Ctrl = control; GRCh38/hg38 = Genome Reference Consortium Human Build 38 Organism: Homo sapiens (human).

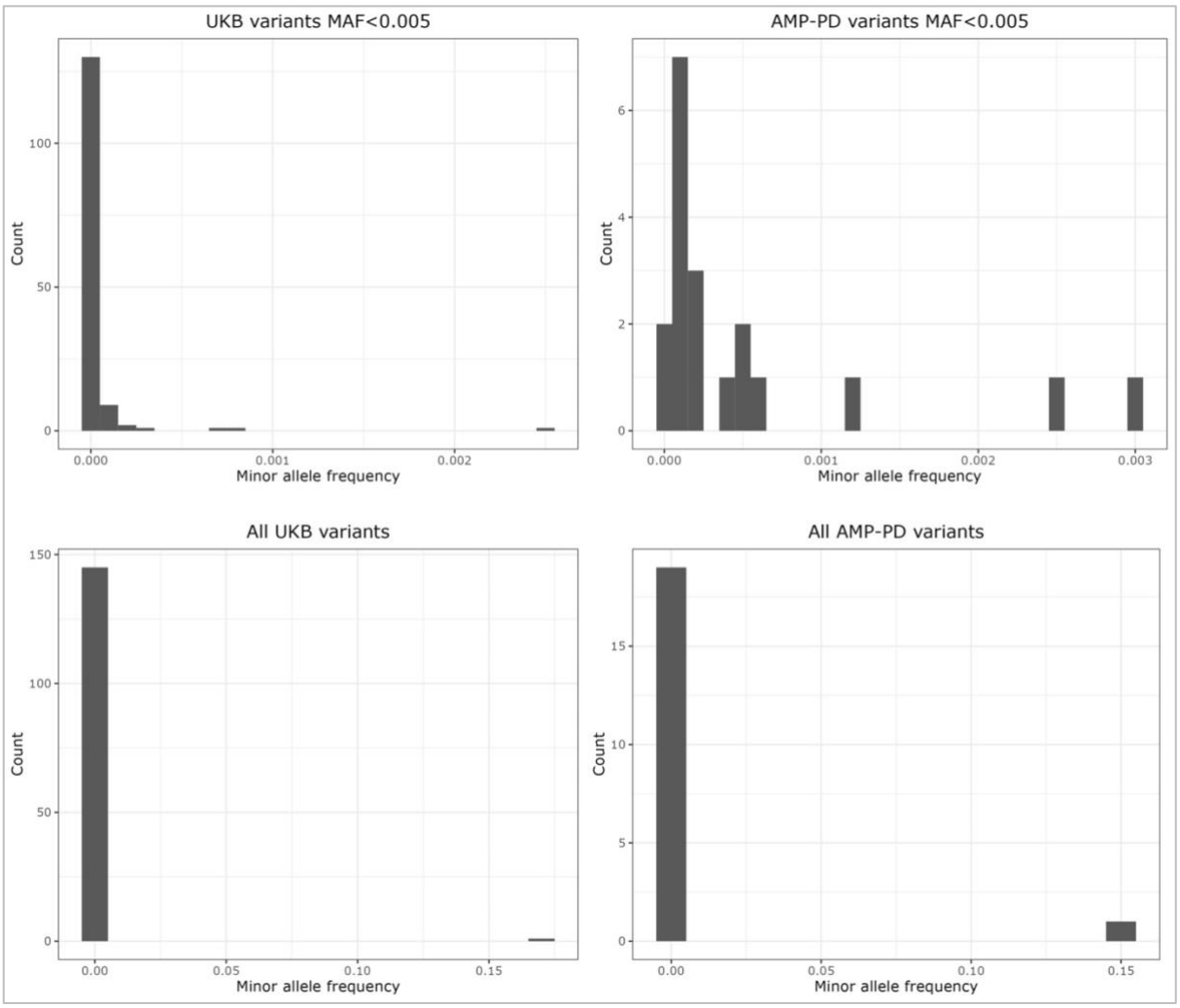
Supplementary File 4. AlphaFold modelling of PSMF1 and FBXO7



Legend: (a) AlphaFold modelling of PSMF1 (UniProt: Q92530) and FBXO7 (Q9Y3I1-1) binding predicted that these two proteins form a heterotetramer. The predicted structures of the models obtained were visualized and analyzed using PyMOL 2.5.5. Predictions consistently showed the same heterodimerization interfaces engaged in binding between PSMF1 and FBXO7 as well as the same homodimerization interfaces of PSMF1, with **(b)** very high pLDDT scores. When analyzing *PSMF1* missense and start-loss variants identified in the study cohort, none of the affected amino acid residues lies at the interface of PSMF1 and FBX07 binding, which makes unlikely for these variants to impact the PSMF1-FBXO7 interaction. The residues p.Leu228 and p.Arg242 are located within the disordered C-terminal region of PSMF1, which makes their impact on binding other proteins difficult to predict. On the contrary, **(c)** the residue p.Leu53 sits on the dimerization interface of PSMF1, forming direct hydrophobic interactions with the residues p.Val6 and p.Ala9 of the second PSMF1 monomer. Based on this prediction, the PSMF1 residue p.Leu53Met (V5 in Fig.1a and Supplementary File 1; Fig.2) identified in Pedigree E could disrupt the binding within the PSMF1 homodimer.

Supplementary File 5. Frequency of *PSMF1* variants in the UK Biobank and the Accelerating Medicines Partnership program for Parkinson's disease (AMP-PD) and gene burden analysis

We searched for *PSMF1* missense (nonsynonymous, nonframeshift indels) and loss-of-function (splice, nonsense, frameshift) variants in the whole-exome sequencing data within the UK Biobank (UKB, (ttps://www.ukbiobank.ac.uk/)[2] and in the whole-genome sequencing data within the Accelerating Medicines Partnership-Parkinson's Disease Initiative (AMP-PD, https://amp-pd.org/).[3] By setting minor allele frequency (MAF) <0.005, we were able to capture most *PSMF1* variants, as documented by the histograms below.



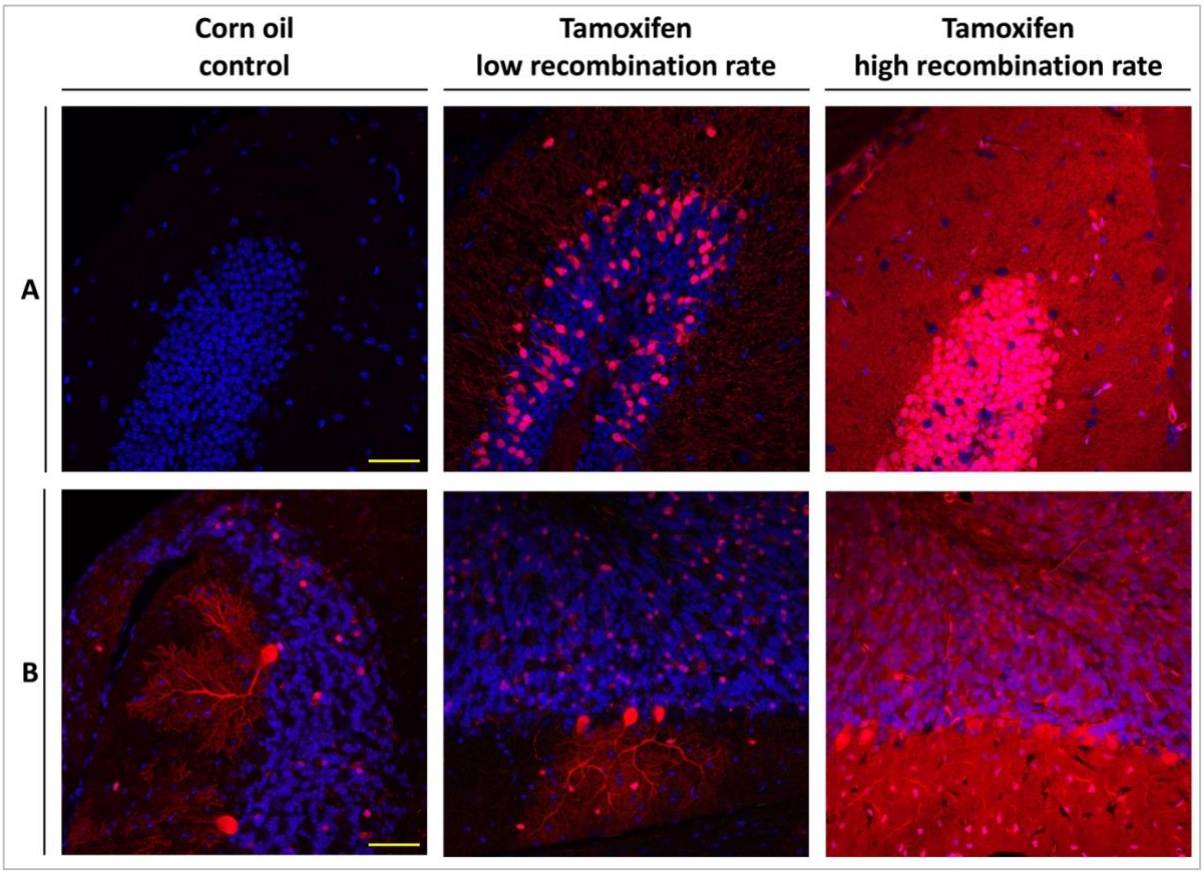
PSMF1 was not significantly associated with Parkinson's disease (PD) in the UKB whole-exome sequencing data and the AMP-PD whole-genome sequencing data, and gene burden analysis revealed that all p values for *PSMF1* in the different categories were >0.05 (not statistically significant).

In UKB, 45,857 people were included (38,051 controls, 1,105 cases, and 6,701 proxies comprised of 6,033 parents and 668 siblings). Using a MAF limit of 0.005, we found 131 missense and 14 loss-of-function variants in *PSMF1*. Single variant association testing (using the --model flag), revealed no association with PD in a recessive model. Specifically, we identified 2 individuals who were homozygotes for a *PSMF1* non-reference allele (genotype=2) in 1/131 variants. Those 2 individuals were 2 controls and 0 cases, resulting in a frequency of 1 for controls. In addition, 560 individuals carried heterozygous non-reference alleles for 1/131 variants, and 2 individuals were heterozygotes for 2/131 variants. Overall, these 562 heterozygous carriers consist of 468 controls and 94 cases, resulting in a frequency of 0.83 for controls and 0.17 for cases, resulting in a 0.66 difference between cases and controls. Using the Sequencing Kernel Association optimal unified test (Skat-O), Combined Multivariate and

Collapsing (CMC) Wald test and CMC burden testing, *PSMF1* resulted in non-significant p values (all *PSMF1* missense variants as defined by ANNOVAR: 0.91 for Skat-O, 0.84 for CMCWald, and 0.84 for CMC; all *PSMF1* missense variants as defined by SnpEff: 0.91 for Skat-O, 0.84 for CMCWald, and 0.84 for CMC). As for *PSMF1* loss-of-function variants in the UKB dataset, we did not identify any homozygous individual for *PSMF1* non-reference alleles in any of the 14 variants. There were 14 heterozygous individuals for 1/19 variants in *PSMF1*. Those 14 heterozygous carriers consisted of 12 controls and 2 cases, resulting in a frequency of 0.86 for controls and 0.14 for cases, corresponding to a 0.72 difference between cases and controls. Using Skat-O, CMCWald, and CMC burden testing, *PSMF1* resulted in non-significant p values (all *PSMF1* loss-of-function variants as defined by ANNOVAR: 0.78 for Skat-O, 0.98 for CMCWald, and 0.98 for CMC; all *PSMF1* loss-of-function variants as defined by SnpEff: 0.48 for Skat-O, 0.30 for CMCWald, and 0.30 for CMC).

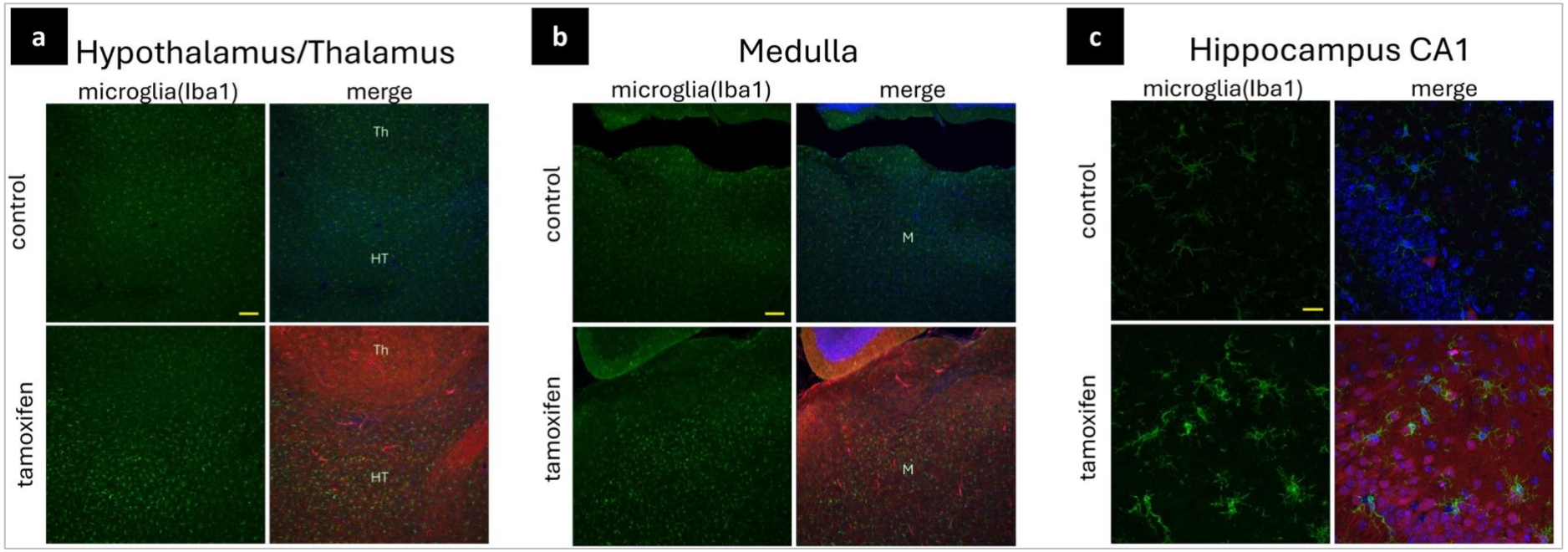
In the AMP-PD, 4,007 people were included (2,556 controls, 1,451 cases). Using an upper MAF of 0.005, we found 19 *PSMF1* missense and no *PSMF1* loss-of-function variants. Single variant association testing (using the --model flag) revealed no associations with PD in a recessive model. As for *PSMF1* variants, we did not identify any individual with a homozygous *PSMF1* non-reference allele in 19 missense variants detected, whereas 83 individuals were heterozygous for 1/19 variants. Those in total 83 heterozygous carriers consisted of 51 controls and 32 cases, resulting in a frequency of 0.61 for controls and 0.39 for cases, thus corresponding to a 0.22 difference between cases and controls. Using Skat-O, CMCWald, and CMC burden testing, *PSMF1* resulted in non-significant p values (all *PSMF1* missense variants as defined by ANNOVAR: 0.21 for Skat-O, 0.95 for CMCWald, and 0.95 for CMC; all *PSMF1* missense variants as defined by SnpEff: 0.27 for Skat-O, 0.572 for CMCWald, and 0.72 for CMC).

Supplementary File 6. TdTomato (red) expression as marker of recombination in brain regions of *Psmf1*$^{fl/fl}$ Ai14 UBC-Cre-ERT2 mice



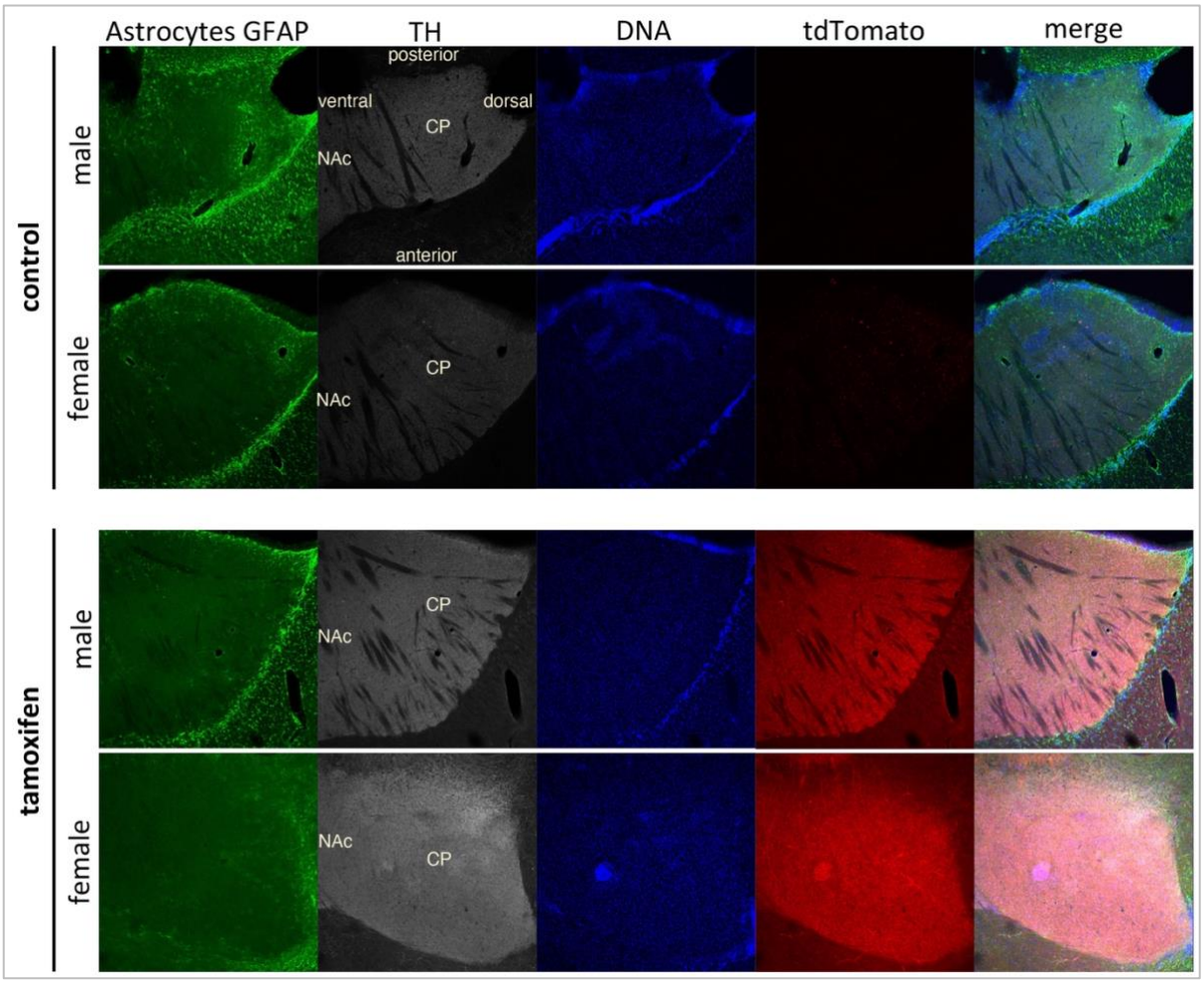
Legend: Tamoxifen-induced recombination in *Psmf1*$^{fl/fl}$ Ai14 UBC-Cre-ERT2 mice induces tdTomato (red) expression, which marks cells in which *Psmf1* is inactivated. Nuclei are stained with Hoechst 33342 (blue). Panels from left to right: control (corn oil), low recombination (tamoxifen; 30-50%) and high recombination (tamoxifen; ~90%). (A) Hippocampus; (B) Cerebellum. Scale bars indicate 50 µm.

Supplementary File 7. Immunohistochemistry of different brain regions of *Psmf1*$^{fl/fl}$ Ai14 UBC-Cre-ERT2 mice 28 days after tamoxifen injection



Legend: *Psmf1*$^{fl/fl}$ Ai14 UBC-Cre-ERT2 mice were injected with either corn oil (control) or tamoxifen to induce Cre recombination of floxed *Psmf1* exon 3 for loss of Psmf1 and a stop cassette in Ai14 for expression of tdTomato (red) to evaluate recombination efficiency. Mice were sacrificed 28 days after tamoxifen injection. Sagittal brain sections were stained with Iba1 (green) for microglia and Hoechst 33342 for nuclei (blue). An increase in reactive microglia was found in the **(a)** hypothalamus (HT) and **(b)** medulla (M) (scale bar 100 µm) as well as in the **(c)** hippocampus CA1 (scale bar 20 µm). Th = thalamus.

Supplementary File 8. Immunohistochemistry of the substantia nigra and ventral tegmental area of *Psmf1*$^{fl/fl}$ Ai14 UBC-Cre-ERT2 mice 28 days after tamoxifen injection



Legend: At Day 28 after tamoxifen injection, there was no evidence of increased gliosis at the axonal ends of tyrosine hydroxylase (TH)-positive dopaminergic neurons in the subortex (striatum: nucleus accumbens [NAc] and caudate putamen [CP]) of *Psmf1*$^{fl/fl}$ Ai14 UBC-Cre-ERT2 mice, as reflected by lack of immunoreactivity for glial fibrillary acidic protein (GFAP) in astrocytes and Iba1 in microglial cells. This could reflect that mice were sacrificed too early for dopaminergic neurons to exhibit pathological phenotype. Nuclei (DNA) were stained with Hoechst 33342 (blue). TdTomato (red) fluorescence was used as indicator of recombination efficiency.

Supplementary File 9. List of primers used for the splicing (minigene) assay of *PSMF1* variants c.365+2T>C and c.605+1G>A (NM_006814.5)

Primer name	Primer sequence (5'-3')	Purpose
hu_PSMF1_Ex3_XhoI_F	aattctcgagATCTCCGTGTTGCTCACCTG	Amplification of gDNA and cloning
hu_PSMF1_Ex3_BamHI_R	attggatccGTGGACTCTTGACTGCACCA	Amplification of gDNA and cloning
hu_PSMF1_Ex5_XhoI_F	aattctcgagTAGGTTTGTGTTCCGCCCTT	Amplification of gDNA and cloning
hu_PSMF1_Ex5_BamHI_R	attggatccACCGGGAAATGGCAGAAGAG	Amplification of gDNA and cloning
PSMF1 c.365+2T_C Mut F	CTTCCACAGGcACTTCTAAATGATGTC	Site-directed mutagenesis
PSMF1 c.365+2T_C Mut R	TCACCCAGGTGTTCTGCA	Site-directed mutagenesis
PSMF1 c.605+1G_A Mut F	ACCCTTTTGGaTGAGTACTGC	Site-directed mutagenesis
PSMF1 c.605+1G_A Mut R	CTAAGTCTTCTCCCCCGA	Site-directed mutagenesis
SD6 F	TCTGAGTCACCTGGACAACC	Colony PCR and RT-PCR
SA2 R	ATCTCAGTGGTATTTGTGAGC	RT-PCR

Legend: gDNA = genomic DNA; PCR = polymerase chain reaction; RT-PCR = real-time (RT) PCR.

Supplementary File 10. CURTAIN web links to proteomics datasets

Figure	Comparison	CURTAIN Web Link
3a	Splice Homozygote vs HC	https://curtain.proteo.info/#/d12eee39-b848-45db-97e9-80e1ed23d4d2
3b	Splice Homozygote vs Missense Homozygote	https://curtain.proteo.info/#/96fc3542-f142-4314-b536-63b0ff2a6ebc
3c	Missense Homozygote vs HC	https://curtain.proteo.info/#/35fdd2ac-0a93-427d-bac0-a54a90a9d67e
3d	Missense Homozygote vs Unaffected Missense Heterozygote	https://curtain.proteo.info/#/393aec7f-1790-466a-abc2-23b8c91af443

Legend: HC = healthy controls.

Supplementary references

1. Quinodoz, M. *et al.* AutoMap is a high performance homozygosity mapping tool using next-generation sequencing data. *Nature Communications* **12**(2021).
2. Bycroft, C. *et al.* The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203-209 (2018).
3. Iwaki, H. *et al.* Accelerating Medicines Partnership: Parkinson's Disease. Genetic Resource. *Mov Disord* **36**, 1795-1804 (2021).