ADDITIONAL FILE 7
SUPPLEMENTARY METHODS

VARIANT CURATION OF ALZHEIMER'S DISEASE ASSOCIATED GENES

- ***APP* Chr21 g.(26253828_30011000)dup.**

Duplication of the APP. Locus have been reported as disease causing for Alzheimer's Disease (AD)[1]

- ***PSEN1* NM_000021, c.349C>G (p.Pro117Ala)**

Variant previously reported in a Colombian family with early onset AD[2].

- ***PSEN1* NM_000021, c.356C>T (p. Thr119Ile) – Figure S16**

Variant previously described as pathogenic. Identified in Argentine[3] and Korean patients with AD[4]

- ***PSEN1* NM_000021, c.428T>C (p. Ile143Thr) – Figure S16**

Variant previously described as pathogenic. Reported in multiple cohorts from different ancestries. European ancestry in Belgium[5] France[6] and Sweden[7]. Asian ancestry in Japan[8] and China[9]. It had also been previously reported in another Colombian family[10].

- ***PSEN1* NM_000021, c.485T>G (p. Ile162Ser) – Figure S16**

ACMG classification: Cosegregation with disease in multiple family members – Figure S16 (ACMG criterion PP1). Absent in population databases – ExAC and 1000 Genomes project (ACMG criterion PM2). More than 300 variants in *PSEN1* have been reported and pathogenic variants in PSEN1 are the most common cause of familiar early onset Alzheimer's disease (https://www.alzforum.org/mutations/psen-1) (ACMG criterion PP2). Predicted to be damaging by three computational algorithms (SIFT CADD and PolyPhen-2) (ACMG criterion PP3) → Likely pathogenic (II)
Guerreiro algorithm for *PSEN1* and *PSEN2* variant classification[11].: Classified as Definite Pathogenic since there are more than three cases of individuals with AD carrying this *PSEN1* variant in the same family

- ***PSEN1* NM_000021, c.488A>G (p. His163Arg) – Figure S16**

Variant previously described as pathogenic. Reported in multiple cohorts from different ancestries, including Americans and Canadians[12], French[13], Japanese [14], Polish[15], Spanish[16], Turkish[17], and Chinese[18].

- ***PSEN1* NM_000021, c.667C>A (p. Gln223Lys) – Figure S16**

ACMG classification: Cosegregation with disease in multiple family members – Figure S16 (ACMG criterion PP1). Absent in population databases – ExAC and 1000 Genomes project (ACMG criterion PM2). Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before[19,20](ACMG criterion PM5). More than 300 variants in *PSEN1* have been reported and pathogenic variants in PSEN1 are the most common cause of familiar early onset Alzheimer's disease (https://www.alzforum.org/mutations/psen-1) (ACMG criterion PP2). Predicted to be damaging by three computational algorithms (SIFT CADD and PolyPhen-2) (ACMG criterion PP3) → Likely pathogenic
Guerreiro algorithm for *PSEN1* and *PSEN2* variant classification[11]: Classified as Definite Pathogenic since there are more than three cases of individuals with AD carrying this *PSEN1* variant in the same family

- ***PSEN1* NM_000021, c.782C>T (p.Val261Ala)**

ACMG classification: Absent in population databases – ExAC and 1000 Genomes project (ACMG criterion PM2). Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before[16,21,22] (ACMG criterion PM5). More than 300 variants in *PSEN1* have been reported and pathogenic variants in PSEN1 are the most common cause of familiar early onset Alzheimer's disease (https://www.alzforum.org/mutations/psen-1) (ACMG criterion PP2). Predicted to be damaging by three computational algorithms (SIFT CADD and PolyPhen-2) (ACMG criterion PP3) → Likely pathogenic

Guerreiro algorithm for *PSEN1* and *PSEN2* variant classification[11]: Classified as probably pathogenic as the variant is seen in a single case, it is absent from population databases, it is conserved between *PSEN1* and *PSEN2* and other pathogenic variants have been described in the same residue.

- ***PSEN1* NM_000021, c.791C>T (p. Pro264Leu) – Figure S16**

Variant previously described as pathogenic. Reported in multiple cohorts from different ancestries, including French[23], British[24] and descendants of the United Kingdom[25], Turkish[17], and Japanese[26].

- ***PSEN1* NM_000021, c.839A>C (p.Glu280Ala)**

Pathogenic variant widely described in Colombian cohorts and a Japanese family[14,27]

- ***PSEN1* NM_000021, c.851C>T (p.Pro284Leu) – Figure S16**

Variant previously described as pathogenic. Reported in a Japanese patient with spastic paraparesis and cotton wool amyloid beta plaques[28].

- ***PSEN1* NM_000021, c.1247T>C (p.Ile416Thr)**

Identified in a Colombian family with early onset AD[29].

- ***PSEN2* NM_000047, c.487C>T (p.Arg163Cys) – Figure S21**

ACMG classification: Previously described in cases with AD. While absent in controls (ACMG criterion PS4)[30]. Absent in population databases – ExAC and 1000 Genomes project (ACMG criterion PM2). Variants in *PSEN2* are a cause of genetic Alzheimer's disease (https://www.alzforum.org/mutations/psen-1) (ACMG criterion PP2). Predicted to be damaging by three computational algorithms (SIFT, CADD and PolyPhen-2) (ACMG criterion PP3) → Likely pathogenic

Guerreiro algorithm for *PSEN1* and *PSEN2* variant classification[11]: Classified as probably pathogenic as the variant is three or more unrelated cases while absent in population databases[30].

VARIANT CURATION OF FTLD-ALS ASSOCIATED GENES

- ***MAPT* NM_005910, c.902C>T (p.Pro301Leu) – Figure S23**

Variant previously described as pathogenic. Reported in multiple cohorts from different ancestries, including Dutch[31], French[32], Spanish[33], Japanese[34], and Chinese[35].

- ***MAPT NM*_005910, c c.1189C>T (p.Pro397Ser) – Figure S23**

Variant previously described as pathogenic. Reported in a cohort of Spanish ancestry[36]

- ***GRN* NM_002087, c.709-2A>G (p.Ala237fs) – Figure S29**

Variant previously described as pathogenic. Reported in multiple cohorts from different ancestries[37,38].

- ***TBK1* NM_002087, c.1257_1258del (p.Val421Cfs*26) – Figure S26**

Loss of function in *TBK1* is a known mechanism for disease[39] (ACMG criterion PVS1). Variant previously documented in Amyotrophic Lateral Sclerosis online (ALS) patients from cohort of European descent[40] (ACMG criterion PS4). Absent in population databases – ExAC and 1000 Genomes project (ACMG criterion PM2). Variant causes a premature stop codon (ACMG criterion PM4)→ Pathogenic

- ***TBK1* NM_002087, c.1717C>T (p.Arg573Cys) – Figure S26**

This variant has previously been reported as dominant non-benign in exome sequencing of ALS patients[41](ACMG criterion PS4). Located in a mutational hotspot or well-studied functional domain [42,43] (ACMG criterion PM1). Missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before[44,45] (ACMG criterion PM5). Segregation data suggests pathogenicity in homozygous carriers (ACMG criterion PP1). Predicted to be damaging by three computational algorithms (SIFT, CADD and PolyPhen-2) (ACMG criterion PP3). → Pathogenic

- ***TARDBP* NM_007375, c.881G>T (p.Gly294Val)**

Variant previously described as pathogenic for ALS. Reported in multiple cohorts from different ancestries, including Italian[36] Morrocan[47,48] and Australian[49]

- ***TARDBP* NM_007375, c.1147A>G (p.Ile383Val) – Figure S28**

Variant previously described as pathogenic. Reported in multiple cohorts from different ancestries, including Sardinian[50], Taiwanese[51], and a cohort of general European descent[40].

VARIANT CURATION OF ALS ASSOCIATED GENES

- ***ANXA11*, NM_001157 c. 904C>T (p.Arg302Cys)**

This variant been reported in individuals with ALS from different cohorts [52,53](ACMG criterion PS4). It is localized in the stabilizing N-terminal segment, where impairs protein function[54] (ACMG criterion PM1). Low rate of benign mutations in a gene associated with the phenotype[55] (ACMG criterion PP2) Predicted damaging by multiple computational methods (CADD, PolyPhen-2, and SIFT) (ACMG criterion PP3) → Pathogenic

- ***FIG4* NM_014845 c.122T>C (p.Ile41Thr)**

The Ile41Thr mutation found in this population has been the most frequent missense mutation associated with CMT4J, an autosomal recessive subtype of Charcot-Marie-Tooth disorders[56].

- ***HNRNPA2B1*, NM_001157 c.965G>A (p.Gly322Glu)**

ACMG classification:

Located in domain has been shown to lead to fibril formation and cause ALS [57,58](ACMG criterion PM1). Absent in population databases – ExAC and 1000 Genomes project (ACMG criterion PM2). Low rate of benign mutations[55] (ACMG criterion PP2). Predicted damaging by multiple computational methods (PolyPhen-2, and SIFT) (ACMG criterion PP3) → Likely Pathogenic

- ***SOD1* NM_000454, c.63C>G (p.Phe21Leu)**

Cell biology studies indicate pathogenicity of this variant [59,60](ACMG criterion PS3). Phe21Leu was reported in a study on ALS in an Italian population[61](ACMG criterion PS4) . Not present in ExAC database (ACMG criterion PM2). Missense variants at Phe21 (misreported in some early papers as being Phe20) have been reported previously in ALS patients[62](ACMG criterion PM5). Low rate of benign mutations in a gene associated with the phenotype[55](ACMG criterion PP2). Predicted damaging in two computational methods (CADD and PolyPhen-2)(ACMG criterion PP3) → Pathogenic

- ***TUBA4A* NM_006000, c.820C>G (p.Pro274Ala) – Figure S32**

Cosegregation with disease in family members of two independent families– Figure S32 (ACMG criterion PP1). Deleterious variation in this gene has been associated with sporadic and familiar ALS[63–65] (ACMG criterion PP2). Predicted damaging by two computational methods (CADD and PolyPhen-2) (ACMG criterion PP3) Absent in population databases – ExAC and 1000 Genomes project (ACMG criterion PM2). → Likely pathogenic

- ***TUBB4A* NM_006087, c.811G>A (p.Ala271Thr)**

Previously described as pathogenic for autosomal dominant motor neuron disease [Clinvar RCV000077783.3]

- ***UBQLN2* NM_001344, c.724G>A (p.Ala242Thr) – Figure 34**

Variant located in STI1 domain, demonstrated to be important for interaction with chaperone proteins and implicated in pathogenesis[66] (ACMG criterion PM1) Absent in population databases – ExAC and 1000 Genomes project (ACMG criterion PM2). Gene with low rate of benign mutations [55](ACMG criterion PP2). Predicted damaging by multiple computational methods (CADD, PolyPhen-2 and SIFT) (ACMG criterion PP3) → Likely pathogenic

VARIANT CURATION OF GENES ASSOCIATED WITH OTHER NEURODEGENERATIVE DISEASES:

- ***CSF1R* NM_001288705, c.2068G>A (p.Gly690Ser) – Figure S36**

This variant is located in the protein kinase domain, which is a hotspot for deleterious mutation [67](ACMG criterion PM1). *CSF1R* has over 60 missense variants reported as pathogenic in patients with Hereditary diffuse leukoencephalopathy with spheroids (HDLD) and cancer predisposition[55] (ACMG criterion PP2). This variant is predicted as damaging by two computational methods (CADD and PolyPhen-2) (ACMG criterion PP3). The patient's phenotype is highly specific for this gene; recurrent malignancies and early onset dementia with neuropathology confirmation of the HDLD diagnosis (ACMG criterion PP4). Family history of dementia and cancer, but with no cosegregation data available for analyses. There is not enough evidence to use the ACMG criteria to declare the variant pathogenic, but the highly specific phenotype of the patient and the family history suggests this variant to be a good candidate to test other family members.

- **DNAJC5 NM_025219, c.347T>G (p.Leu116Arg) – Figure S35**

DNAJC5 has been implicated as pathogenic for neuronal ceroid lipofuscinosis of adult onset (CLN4B) with a low rate of benign variation(ACMG criterion PP2). Functional studies of the residue Leu116 support the pathogenicity of variants in that residue[68](ACMG criterion PS3). Leu116Arg is located in a mutational hotspot for CLN4B [69–71] (ACMG criterion PM1). Leu115Arg and Leu116del mutations were originally discovered in a study done on a Czech family along with data from previous patients collected from the

Netherlands, USA, Canada, France, Italy, Germany, Austria, Belgium and Poland[72] (ACMG criterion PM5). Absent in population databases – ExAC and 1000 Genomes project (ACMG criterion PM2). Predicted to be at least possibly damaging by multiple computational methods (CADD, PolyPhen-2 and SIFT) (ACMG criterion PP3). The phenotype and cosegregation of the variant with the illness supports the diagnosis of CLN4B and pathogenicity of the variant (ACMG criteria PP4 and PP1-S) → Pathogenic

- ***LRRK2* NM_198578, c.4334C>G (p.Ser1445Cys)**

Functional studies have demonstrated that Ser1445 is one of LRRK2 autophosphorylation sites, where missense mutations are deleterious[73–75] (ACMG criterion PS3). Located in the Roc (GTP-ase like) domain which is a mutational hotspot (Uniprot database Q5S007 and [76]) (ACMG criterion PM1). Absent in population databases – ExAC and 1000 Genomes project (ACMG criterion PM2). Predicted as damaging by two computational methods (CADD and PolyPhen-2) (ACMG criterion PP3) → Likely pathogenic

- ***LRRK2* NM_198578, c.6055G>A (p.Gly2019Ser)**

The G2019S mutation has been discovered to be the most frequent cause of autosomal dominant PD in many genome and exome sequencing studies within a wide variety of populations [77–79].

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