

Genome sequencing for early-onset dementia: high diagnostic yield and frequent observation of multiple contributory alleles

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Running title: Utility of early-onset dementia genome sequencing

ABSTRACT

We assessed the utility of genome sequencing for early-onset dementia. Participants were selected from a memory disorders clinic. Genome sequencing was performed along with *C9orf72* repeat expansion testing. All returned sequencing results were Sanger validated clinically. Prior clinical diagnoses included Alzheimer's disease, frontotemporal dementia, and unspecified dementia. The mean age-of-onset was 54 (41–76). 50% of patients had a strong family history, 37.5% had some, and 12.5% had no known family history. Nine of 32 patients (28%) had a variant defined as pathogenic or likely pathogenic (P/LP) by American College of Medical Genetics standards, including variants in *APP*, *C9orf72*, *CSF1R*, and *MAPT*. Nine patients (including three with P/LP variants) harbored established risk alleles with moderate penetrance (odds ratios of about 2–5) in *ABCA7*, *AKAP9*, *GBA*, *PLD3*, *SORL1*, and *TREM2*. All six patients harboring these moderate penetrance variants but not P/LP variants also had one or two *APOE* ϵ 4 alleles. One patient had two *APOE* ϵ 4 alleles with no other established contributors. In total, 16 patients (50%) harbored one or more genetic variants likely to explain symptoms. We identified variants of uncertain significance (VUSs) in *ABI3*, *ADAM10*, *ARSA*, *GRID2IP*, *MME*, *NOTCH3*, *PLCD1*, *PSEN1*, *TM2D3*, *TNK1*, *TTC3*, and *VPS13C*, also often along with other variants. In summary, genome sequencing for early-onset dementia demonstrated high utility, with particular advantages where targeted testing may fail such as atypical variant-disease associations or presence of multiple moderate impact alleles. One or more established contributory alleles is often present in early-onset dementia, supporting an oligogenic model.

INTRODUCTION

Genomic technologies are increasingly being used in clinical settings, but clinical large-scale sequencing for adult-onset neurological conditions has not been heavily applied. Possible reasons include the use of disease-specific gene panels and uncertain genetic yield, despite promising signals for yield using comprehensive approaches (Blauwendraat et al. 2018). We sought to assess the diagnostic yield with genome sequencing and *C9orf72* expansion testing in cases of early-onset dementia.

Patients were selected from the Memory Disorders Clinic at the University of Alabama at Birmingham (UAB). Inclusion criteria were clinician-diagnosed early-onset dementia. When possible, unaffected parents were included as participants to allow filtering for *de novo* variants in patients without a family history (a fruitful approach in pediatric genetic disorders (Vissers et al. 2010; Bowling et al. 2017) and amyotrophic lateral sclerosis (ALS) (Chesi et al. 2013; Steinberg et al. 2015a)). In addition, unaffected siblings past the age of onset of the patient were enrolled as participants when possible for variant filtering and segregation.

Before starting analysis, we set criteria for return of results to patients. First, we used the American College of Medical Genetics (ACMG) criteria for pathogenicity (Richards et al. 2015) to identify highly penetrant causal variation. For moderately penetrant variants, we set criteria to return: (i) *APOE* ϵ 4 status for early-onset Alzheimer's disease (EOAD), (ii) any variant with a disease-associated odds ratio greater than two in multiple reports as an "established risk variant," or (iii) one strong report with a disease-associated odds ratio greater than two with replication included in the study design as a "likely risk variant."

RESULTS

Clinical presentation and family history

Prior clinical diagnoses for patients included EOAD, frontotemporal dementia (FTD), and other unspecified dementias. 21 patients were female and 11 were male. 28 self-reported Caucasian and four self-reported African American, all reported non-Hispanic ethnicity. The mean age of onset was 54

(range 41–76). 10 patients had ages of onset in their 40's, 17 in their 50's, 4 in their 60's, and 1 in their 70's.

In addition to enrolling patients, we also enrolled reportedly unaffected family members for variant filtering and segregation analyses. 31 unaffected relatives were enrolled, 29 of which had genome sequencing (2 were only checked for variants by Sanger). Only two families had complete trios (mother, father, and proband) to allow for searching for *de novo* variants, of which none of interest were identified. In total, 20 unaffected siblings, 9 unaffected parents, and 2 unaffected cousins were enrolled.

A strong family history of dementia was reported for 50% of patients (16/32), while 37.5% (12/32) had some family history, and 12.5% (4/32) had no reported family history. Our definition of family history is based on a modification of a four point scoring system first put forward by Jill Goldman (Goldman et al. 2005) where we modified the score as follows: (1) At least three people in two generations affected with EOAD, FTL, ALS, CBD, or PSP with one person being a first-degree relative of the other two, (1.5) Same as (1) but with LOAD instead of EOAD, (2) At least three relatives with dementia or ALS but where criteria for autosomal dominant inheritance were not met, (3) A single affected first or second degree family member with early-onset dementia or ALS, (3.5) A single affected first or second degree family member with late-onset dementia or ALS, (4) No contributory family history or unknown family history. We considered a score of 1 or 1.5 as strong family history, a score of 2, 3, or 3.5 as some family history, and a score of 4 as no reported family history. All family history information is listed alongside phenotype and variant information in **Supplemental Table 1**.

To protect patient information, more detailed diagnoses and phenotype information beyond that provided here and listed in **Supplemental Table 1** are only provided in the controlled access dataset, NIAGADS project NG00082, to qualified researchers approved for access.

Genomic analyses

Nine of 32 (28%) patients had a highly penetrant variant relevant to their clinical diagnosis (ACMG P/LP (Richards et al. 2015)), while seven (22%) had multiple moderately penetrant risk alleles (**Figure 1**). Individual cases are discussed next, with variants identified summarized by **Table 1** and listed alongside phenotype information in **Supplemental Table 1**.

Pathogenic or Likely Pathogenic Diagnoses

Variants were first evaluated using ACMG criteria for pathogenicity, and all P/LP variants were returned to patients (Richards et al. 2015). We provide a summary below, with detail on the ACMG evidence codes for variants provided in the Supplemental ACMG Pathogenicity Evidence Details.

APP Pathogenic Variant (V717F) in Two Siblings

Two siblings with ages of onset in the mid-to-late 40s and a family history of EOAD suggestive of dominant inheritance harbored a pathogenic variant in *APP* (NM_000484.3, c.2149G>T, V717F), a well-established pathogenic variant (see Supplemental ACMG Pathogenicity Evidence Details). This variant is an example of one that would have been identified on commonly-used panels for genetic testing for EOAD.

C9orf72 Expansion Carriers

Testing for a pathogenic G₄C₂ hexanucleotide expansion at the *C9orf72* locus associated with ALS and FTD was ordered for 30 of 32 patients (with two excluded for technical reasons, see Methods). GeneDx conducted a repeat-primed PCR test with 95% sensitivity and 98% specificity (Akimoto et al. 2014) to detect *C9orf72* expansions. As a technical aside, *C9orf72* expansions were not detectable using ExpansionHunter (Dolzhenko et al. 2017) or STRetch (Dashnow et al. 2018) in genome sequencing libraries prepared with PCR amplification assessed here. ExpansionHunter detects *C9orf72* expansions in PCR-free genome preparations (Dolzhenko et al. 2017), so PCR-free genome preparations or secondary testing (such as testing conducted by GeneDx for here) is necessary for detection of *C9orf72* expansions (and would also be necessary for other repeat expansions). Three patients with FTD (one patient also had ALS signs) with ages-of-onset in the 40s and 50s harbored a pathogenic expansion in *C9orf72* (see Supplemental ACMG Pathogenicity Evidence Details).

Some studies have suggested that additional contributing alleles could lower age of onset and/or alter clinical presentation for *C9orf72* expansion carriers (van Blitterswijk et al. 2012; van

Blitterswijk et al. 2014; Pottier et al. 2015; Giannoccaro et al. 2017; Farhan et al. 2018). Consistent with this, all three *C9orf72* expansion carriers harbored other possibly contributory variants.

One carrier had three additional variants that may be contributory: an “established risk” stop gained variant in *ABCA7* (NM_019112.3, c.5035G>T, p.E1679*), one *APOE* ε4 allele, and a VUS in *PSEN1* (NM_000021.3, c.103C>T, p.R35W) (see Supplemental ACMG Pathogenicity Evidence Details). These variants may have contributed to the patient’s family history of multiple neurodegenerative diseases including ALS and EOAD.

Another carrier had a different “established risk” variant in *ABCA7* (NM_019112.3, c.2126_2132delAGCAGGG, p.E709Afs*86) (see Supplemental ACMG Pathogenicity Evidence Details), along with memory symptoms and a family history of AD, consistent with a possible contributory role of *ABCA7*.

The third carrier had two VUS in *ARSA*, associated with recessive metachromatic leukodystrophy (discussed further in Supplemental ACMG Pathogenicity Evidence Details).

MAPT R406W Pathogenic Variant in Three Alzheimer’s Disease Patients

Three patients with EOAD (one patient also exhibited FTD signs) with ages-of-onset in the mid 50s to early 60s harbored a pathogenic variant in *MAPT* (NM_005910.5, c.1216C>T, p.R406W). Although *MAPT* pathogenic variants are typically associated with FTD (Cruts et al. 2012), this variant has been reported in patients with clinically diagnosed Alzheimer’s disease (AD) in multiple studies (see Supplemental ACMG Pathogenicity Evidence Details). This variant would not have been detected on many AD-specific panels, which often test for only *APP*, *PSEN1*, and *PSEN2*.

All three of these patients exhibited a possible contribution from another allele, just as in *C9orf72* expansion carriers. One patient had a loss-of-function “established risk” variant in *ABCA7* (NM_019112.3, c.2126_2132delAGCAGGG, p.E709Afs*86). Another patient had a VUS in *APP* (NM_000484.3, c.1090C>T, p.L364F). The third patient had a loss-of-function splice variant in *GRID2IP* (NM_001145118.1, c.429+2T>G), which, while not yet firmly associated with EOAD and thus not yet returnable, was implicated in a recent large sequencing study (Raghavan et al. 2018).

The presence of this rare variant in three individuals enrolled at the same clinic suggests they may share a common ancestor. However, none of these individuals are aware of any extended family members participating in the study. Furthermore, the patients are not detectably related by software used for routine checks of close familial relationships (KING).

CSF1R R900K in an FTD Patient

A patient presenting with behavioral variant FTD (bvFTD) harbored a likely pathogenic variant in *CSF1R* (NM_005211.3, c.2699G>A, p.R900K) (see Supplemental ACMG Pathogenicity Evidence Details). Patients with variants in *CSF1R* can present with bvFTD, but the underlying pathology of pathogenic *CSF1R* variants is leukoencephalopathy (Rademakers et al. 2011; Stabile et al. 2016). Consistent with this, this patient had white matter abnormalities on MRI with frontal-predominant confluent white matter hyperintensity (**Figure 2A**) and global atrophy (**Figure 2B–D**). This variant would not have been detected on typical panels testing for FTD.

High Impact Risk Alleles

One unique aspect of this study is that we returned to patients moderately penetrant risk variants that meet criteria we have described. Intriguingly, rare variants meeting these criteria were observed only along with one or two *APOE* ϵ 4 alleles, the most common moderately penetrant risk allele for AD (see Supplemental ACMG Pathogenicity Evidence Details). In all cases, *APOE* ϵ 4 alleles were returned as “established risk variants.” The presence of one *APOE* ϵ 4 allele was returned as likely only a small contributor to symptoms, while presence of two *APOE* ϵ 4 alleles or one or two *APOE* ϵ 4 alleles in combination with a rare moderately penetrant risk variant was returned with language indicating that such a combination of variants is likely to explain a large portion of the genetic contribution to symptoms (but with the caveat that family members should not be presymptomatically tested given incomplete penetrance). We continue with detail on some cases falling into this category.

A case with APOE ε4 Homozygosity, PLD3 V232M, APP D248N, and ABI3 V97E

In a patient with EOAD whose symptoms began in the late 40s with enrolled unaffected parents, we observed an example of how EOAD may occur from a combination of inherited alleles from each parent, consistent with previous observations that EOAD can appear recessive in nature (Wingo et al. 2012). The patient had two *APOE* ε4 alleles (returned as “established risk,”) a *PLD3* variant (NM_012268.3, c.694G>A, p.V232M) (returned as “likely risk,”) an *APP* variant (NM_000484.3, c.742G>A, p.D248N) (returned as a VUS), and a private variant in *ABI3* (NM_016428.2, c.290T>A, p.V97E) (not returned but predicted damaging by PolyPhen-2 (Adzhubei et al. 2010) and SIFT (Ng and Henikoff 2003), with a CADD score (Kircher et al. 2014) of 33) (see Supplemental ACMG Pathogenicity Evidence Details). The *ABI3* variant was not returned to the patient because of insufficient evidence to consider the variant as a returnable VUS or risk variant, but is highlighted because a different coding variant in *ABI3* (NM_012268.3, c.1124T>C, p.S209F) (Sims et al. 2017) was associated with AD in a rigorous case-control study with an odds ratio of 1.4, yet is not predicted to be as damaging (CADD=13.5) and is relatively common in population databases (allele frequency of 0.6%). Therefore, we speculate that perhaps the variant we observed could have an effect of similar or greater magnitude given its higher predicted deleteriousness and absence from population databases. One of the *APOE* ε4 alleles and the variants in *PLD3* and *APP* was inherited from a parent with neurologic symptoms but not EOAD. The other parent harbored an *APOE* ε4 allele and the *ABI3* variant and did not have neurologic symptoms. This case serves as an example of how EOAD may arise with either no family history or limited family history of late-onset disease.

A case with APOE ε4 Heterozygosity and SORL1 M105T

An individual with EOAD with onset in the mid 50s and a strong family history of AD had one *APOE* ε4 allele and a variant in *SORL1* (NM_003105.5, c.314T>C, p.M105T). While *SORL1* variants are not completely penetrant, loss-of-function variants in *SORL1* confer one of the highest levels of risk for AD outside of dominant pathogenic variants and *APOE*. Loss-of-function *SORL1* variant carriers in cases from a recent study (Raghavan et al. 2018) are present at an odds ratio of about four compared to population databases, a likely underestimate given that some individuals in population databases

may develop AD. Indeed, a recent meta-analysis suggests the odds ratio for loss-of-function *SORL1* variants could be as high as 12.3 for all AD and 27.5 for EOAD (Campion et al. 2019).

For the *SORL1* variant identified here, we checked independent datasets for replication, and observed one M105T carrier in one study (Sassi et al. 2016), three M105T carriers in Alzheimer's Disease Sequencing Project (ADSP) exomes (Bis et al. 2018), and two M105T carriers in ADSP genomes (one in an AD case and in one a mild cognitive impairment case) with no controls harboring the variant in any of these datasets. No other carriers were identified in cases or controls in four other studies (see Supplemental ACMG Pathogenicity Evidence Details). In addition to these four studies, there is one record in ClinVar from GeneDx (RCV000489328.1), but it lacked a denominator of the number of cases tested and thus was not considered in calculating the replication statistic. Taken together, *SORL1* M105T is observed six times out of 13,390 AD cases compared to 11 of 189,196 individuals at a population level for a replication-only odds ratio of 7.7 ($p = 0.0005$ by Fisher's exact test). This variant did not completely segregate with disease in four family members of our patient. However, the age-of-onset range for similar variants in *SORL1* can be up to 24 years (Louwersheimer et al. 2017), which is wider than the age differences between the family members we genotyped, suggesting that this segregation analysis may not be completely informative. Considering all of the evidence, we returned this variant to the patient as a VUS (it could also be considered a "likely risk variant"). Modelling suggests M105T is a highly conserved residue (**Figure 3A**) where change to a threonine may create a PLK1 kinase site that may disrupt function (**Figure 3B**) (discussed further in Supplemental ACMG Pathogenicity Evidence Details).

APOE ε4 with TREM2, AKAP9, and GBA Risk Variants

In two cases with EOAD beginning in the late 40s, we observed a risk allele in *TREM2* and one or two *APOE ε4* alleles. The first was *TREM2* (NM_018965.3, c.140G>A, p.R47H) (Guerreiro et al. 2013; Jonsson et al. 2013) with one *APOE ε4* allele. This *TREM2* variant was returned as an "established risk variant." Second, we observed *TREM2* (NM_018965.3, c.259G>A, p.D87N) (Guerreiro et al. 2013) (see Supplemental ACMG Pathogenicity Evidence Details) with two *APOE ε4* alleles. This *TREM2* variant was returned as a "likely risk variant."

In an African American patient with features of both EOAD and FTD, we observed a variant in *AKAP9* previously reported to increase risk in African Americans (NM_005751.4, c.7638A>G, p.I2546M) (Logue et al. 2014). In this case, despite only being observed in one study with replication, the specificity of this variant disease association to African American ethnicity and additional functional data (Ikezu et al. 2018) provided enough evidence to return this as an “established risk variant.”

A patient with EOAD with onset in the mid 50s harbored *GBA* (NM_000157.3, c.1448T>C, p.L483P [previous nomenclature, p.L444P]) and two *APOE* $\epsilon 4$ alleles, originally associated with Lewy body disorders (Mata et al. 2008), but later also with mixed Dementia with Lewy Bodies and AD (Tsuang et al. 2012; Nalls et al. 2013). Because of this and a recent association with accelerated cognitive decline (Liu et al. 2016), we returned this as a “likely risk variant.”

VPS13C loss-of-function with *APOE* $\epsilon 4$

A patient with mixed symptoms of AD and FTD with onset in the late 60s harbored *VPS13C* (NM_020821.2, c.10954C>T, p.R3652*) and two *APOE* $\epsilon 4$ alleles. A patient with EOAD with onset in the late 40s had *VPS13C* (NM_020821.2, c.1988delC, p.T663Nfs*2), a variant in *PLCD1* (NM_006225.3, c.631C>T, p.R211W), and one *APOE* $\epsilon 4$ allele. Only *APOE* $\epsilon 4$ was reported back to these patients because of uncertain contribution of the other variants to the phenotype. Homozygous loss of *VPS13C* is associated with early-onset Parkinson’s (Schormair et al. 2018). We do not know the significance of the observation of one loss-of-function allele here, although unpublished studies have reported an association between heterozygous loss-of-function in *VPS13C* and FTD (see Supplemental ACMG Pathogenicity Evidence Details). *PLCD1* was proposed as a candidate gene for AD in one study (Shimohama et al. 1998). Observing two loss-of-function variants in *VPS13C* in this small cohort leads us to speculate that heterozygous loss-of-function variants in *VPS13C* may contribute to early-onset dementia.

Variants of Uncertain Significance or Research Interest

Five other patients harbored interesting – but speculative – VUSs or combinations of variants of interest for future research. These include (1) a patient with possible CADASIL and a haplotype of

uncertain significance with two variants in *NOTCH3* (NM_000435.2, c.133G>C, p.D45H and NM_000435.2, c.154G>A, p.G52R), (2) a patient with a VUS in *MAPT* (NM_005910.5, c.1174A>G, p.I392V), (3) a patient with an *APOE* ϵ 4 allele and a variant in both *ADAM10* (NM_001110.3, c.359T>C, p.I120T) and *TTC3* (NM_001001894.2, c.5557G>A, p.V1853M), (4) a patient with an *APOE* ϵ 4 allele, and a variant in both *SORL1* (NM_003105.5, c.1247G>A, p.R416Q) and *MME* (NM_007289.2, c.1241A>G, p.Y414C), and (5) a patient with variants in *TM2D3* (NM_078474.2, c.206C>T, p.P69L) and *TNK1* (NM_001251902.1, c.393C>G, p.H131Q). Furthermore, one patient harbored a secondary pathogenic variant in *KCNQ1* (NM_000218.2, c.1552C>T, R518*). We expand on these cases in the Supplemental ACMG Pathogenicity Evidence Details.

Quantitative Enrichment of Multiple Alleles

Because we observed so many cases harboring multiple established alleles, we asked if this effect was statistically enriched over a control population recruited from the same geographical area, with controls reporting a family history of dementia excluded. We set criteria for qualifying variants as follows: (1) *TREM2* or *GBA* missense or loss-of-function variants with CADD>20 and population frequency <0.5% in both gnomAD (Lek et al. 2016) and TOPMed Bravo (NHLBI 2018), (2) *ABCA7*, *SORL1*, *TBK1*, or *GRN* loss-of-function variants with CADD>20 and population frequency <0.5%, (3) the specific *PLD3* and *AKAP9* variants observed here (since their associations are for single alleles), (4) missense only variants with CADD>20 and population frequency <0.01% for *SORL1*, *CSF1R*, *APP*, *PSEN1*, *PSEN2*, and *MAPT*, (5) expansion carriers in *C9orf72*, and (6) *APOE* ϵ 4 alleles. We recognize that this may contain bias since these filtering criteria were selected after analysis of cases. However, we attempted to mitigate this by selecting reasonable thresholds that would catch variants not identified in this study but that would still have been considered if they had been identified. For example, we did not observe any variants meeting these criteria in *TBK1* or *GRN* but included them here because of their important role in disease. We also included *C9orf72* carriers without information on if any are present in the control population, but this is a reasonable assumption (see Supplemental ACMG Pathogenicity Evidence Details).

287 Variants meeting the criteria described are highly enriched in cases (**Figure 4A**). Intriguingly,
288 there is no enrichment of *APOE* ϵ 4 alleles in the absence of other qualifying alleles (**Figure 4B**). In
289 contrast, the presence of *APOE* ϵ 4 alleles in combination with another qualifying variant is highly
290 enriched in cases, regardless of whether Mendelian variants are included in the calculation (**Figure 4C**)
291 or excluded (**Figure 4D**). The odds ratios for *APOE* ϵ 4 alleles in combination with another qualifying
292 variant in cases without a Mendelian cause suggests that the presence of rare variants increases odds
293 ratios approximately multiplicatively over those typically reported for *APOE* ϵ 4 alone (typically reported:
294 ~2.5 for one *APOE* ϵ 4 allele, with a rare variant, 5.5; 10–15 for two *APOE* ϵ 4 alleles, with a rare variant,
295 39.1), see Supplemental ACMG Pathogenicity Evidence Details on *APOE*) (**Figure 4D**).

297 DISCUSSION

298 One key theme in this study was the frequent observation of multiple possible contributory
299 alleles. We even observed this in multiple cases with clear, highly penetrant, pathogenic variants
300 despite a small cohort size. The degree to which additional alleles contribute in dominant cases cannot
301 be assessed without larger cohorts to evaluate effects on age-of-onset or other variables. However,
302 given that other studies have made similar observations in ALS/FTD (van Blitterswijk et al. 2012; van
303 Blitterswijk et al. 2014; Pottier et al. 2015; Giannoccaro et al. 2017; Farhan et al. 2018), this
304 phenomenon clearly warrants further investigation.

305 In cases where a dominant pathogenic variant was not present, there was enrichment for
306 multiple established alleles contributing to disease risk. Every case with a moderately penetrant risk
307 variant established by case-control studies identified in this cohort also harbored one or two *APOE* ϵ 4
308 alleles, emphasizing the importance of *APOE* ϵ 4. Future efforts in analysis of large cohorts should
309 include analysis of level of risk when rare risk variants are present, for example by incorporation of
310 signal from rare variation in established risk genes into polygenic risk scores. Several groups have
311 begun developing polygenic risk scores for AD (Escott-Price et al. 2015; Desikan et al. 2017), but these
312 scores are based solely on common variation. This is, of course, a reasonable approach because it
313 maximizes reproducibility, as considering rare variants could lead to an over-trained model. However,
314 while rare variants are rare individually, aggregation approaches may provide replicable and meaningful

signals if incorporated for key genes where rare variants are now established to confer risk for AD, such as *ABCA7*, *SORL1*, and *TREM2*. Similarly, while large FTD genetic studies are not as progressed as those for AD, we can begin to consider genes where variation in a polygenic risk score may be informative for FTD, such as *TBK1* (Cirulli et al. 2015), *MFSD8* (Geier et al. 2019), *DPP6*, *UNC13A*, and *HLA-DQA2* (Pottier et al. 2019).

In Conclusion, this study demonstrates the high diagnostic and research utility of genome sequencing in cases of early-onset dementia. Mendelian diagnostic yield in this population was 28%, with an additional 22% of patients harboring risk-increasing variants that, in combination with *APOE* $\epsilon 4$, likely account for most of the genetic contribution to their symptoms. Genome sequencing is able to identify relevant variation in conditions with high genetic heterogeneity, nonspecific phenotypes, or established risk factors that do not follow a clear Mendelian pattern, and allowed for identification of cryptic genotype-phenotype relationships that likely would have been missed by panel testing. In addition to the research value of this study, it had value for patient care as well, for example by allowing for referral of families to the Dominantly Inherited Alzheimer's Network and the Advancing Research & Treatment for Frontotemporal Lobar Degeneration study. We conclude that application of more comprehensive genetic testing (including genome sequencing, where appropriate) could aid in evaluation of early-onset dementia cases currently and will continue to grow in utility for future use.

METHODS

Genome sequencing

Genome sequencing was performed at the HudsonAlpha Institute for Biotechnology on Illumina HiSeq X or NovaSeq platforms using paired end 150 base pair reads. Mean depth was 34X with an average of 91.5% of bases covered at 20X. Sequencing libraries were prepared by Covaris shearing, end repair, adapter ligation, and PCR using standard protocols. Library concentrations were normalized using KAPA qPCR prior to sequencing. All sequencing variants returned to patients were validated by CAP/CLIA Sanger.

Data processing and quality control

Demuxed FASTQs were aligned with bwa-0.7.12 (Li and Durbin 2009) to hg19. BAMs were sorted and duplicates were marked with Sambamba 0.5.4 (Tarasov et al. 2015). Indels were realigned, bases were recalibrated, and gVCFs were generated with GATK 3.3 (McKenna et al. 2010). gVCFs were batch called with GATK 3.8. KING 2.1.2 (Manichaikul et al. 2010) was used for sex checks on VCFs, for validation of known familial relationships, and to check for unknown familial relationships (none of which were identified).

C9orf72 expansion testing

Samples from 30 of 32 patients were tested for pathogenic *C9orf72* repeat expansion alleles by GeneDx (Gaithersburg, MD). Two patients did not have sufficient material for testing, but both lacked symptoms consistent with a *C9orf72* repeat expansion and also had another likely explanation of symptoms: one had a pathogenic *APP* variant and another harbored both one *APOE* ϵ 4 allele and a *TREM2* established risk allele).

Genomic data analysis

The HudsonAlpha-developed Codicem application (<http://envisiongenomics.com/codicem-analysis-platform/>) was used to analyze and support interpretation of the variant data (described elsewhere (Holt et al. 2019)). Although this software package was used for analysis, it would not be necessary to use this package to reproduce this work. Simple filtering for population allele frequencies (ie gnomAD (Lek et al. 2016) and TOPMed Bravo (NHLBI 2018)), *in silico* deleteriousness scores (ie CADD (Kircher et al. 2014), PolyPhen-2 (Adzhubei et al. 2010), and SIFT (Ng and Henikoff 2003)), and gene lists relevant to the phenotype of interest would recapitulate our findings using any suitable software package, or even by a command line interface.

In addition to searching for single nucleotide variants and small indels, we also searched for large copy number variations using four callers (DELLY (Rausch et al. 2012), ERDS (Zhu et al. 2012), CNVnator (Abyzov et al. 2011), and BIC-seq2 (Xi et al. 2016)), but did not identify any relevant to patient phenotypes (including absence of *APP* duplications).

SORL1 structural modeling

SORL1 structural modeling and evolutionary conservation analysis was assessed using a previously published sequence-to-structure-to-function workflow (Prokop et al. 2017).

Statistics

The exact conditional Cochran-Armitage trend test was calculated using the CATTexact 0.1.0 package and Fisher's exact test using fisher.test in R 3.4.1.

Return of results

Results meeting criteria for return were delivered to patients by clinicians in the UAB Memory Disorders Clinic through letters written by a genetic counselor. Letters included information on the variant, associated disease, recurrence risk, and management recommendations. Patients were given the option to have a genetic counselor present for return of results via phone or videoconference or to follow up with a genetic counselor after delivery of results. Primary results were provided only to probands. Although a secondary result was identified in only one participant who was a patient, we did also offer non-patient participants (family members) receipt of actionable secondary findings (ACMG 59™) if such a result had been identified. Family members of patients that received diagnostic results were provided with information to seek out clinical genetic counseling and targeted testing for familial variants if they desired.

ADDITIONAL INFORMATION

Data Deposition and Access

All data from participants enrolled as a part of this study, including more detailed phenotype data for the cases described here, are available on the National Institute on Aging Genetics of Alzheimer's Disease Data Storage (NIAGADS) site under project NG00082. Data from control subjects not enrolled as a part of this study are available under dbGaP accession phs001089.v3.p1, which contains data generated by the Clinical Sequencing Exploratory Research (CSER) Consortium

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ADNI (Alzheimer's Disease Neuroimaging Initiative, part of the ADSP genomes batch call) and ADSP data are available at NIAGADS under projects NG00066 and NG00067 and on dbGap under accession phs000572.v7.p4 (see Supplemental Extended Acknowledgements for full list of ADNI and ADSP contributors and funding sources).

Ethics Statement

This study was approved by UAB IRB protocol X161202004, "Evaluation of Genomic Variants in Patients with Neurologic Diseases." All participants described provided explicit written consent for publication.

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Authors' contributions

JNC, GMC, RMM, and EDR designed the study. JNC and RMM secured funding. JNC and EDR wrote the IRB protocol. ECM coordinated all aspects of patient interaction. JNC, MDA, BAM, and BNL analyzed genomes with input from MEC, ECM, and EDR. MDA coordinated *C9orf72* testing. JNC,

DEG, JM JL, JWP, EGG, JMH, and JSN conducted other analyses. MEC wrote clinical letters and provided genetic counseling. MLT provided phenotype information for controls. JSY accessed ADSP and supervised EGG. EAW supervised JMH, JSN, and the software development team. EDR, DSG and MNL recruited participants and returned results. GMC supervised DEG, JM JL, and MLT. JNC wrote the manuscript, with edits by ECM, MEC, MDA, BAM, BNL, JWP, EGG, JMH, EAW, GMC, and EDR. All authors approved the final manuscript.

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SUPPLEMENTAL MATERIAL

ACMG Pathogenicity Evidence Details:

APP (NM_000484.3, c.2149G>T, V717F).

Two strong criteria, three moderate criteria, and one supporting criterion result in the ACMG-recommended assertion of “pathogenic.”

- Strong segregation data (Murrell et al. 1991; Finckh et al. 2005) (ACMG criterion PP1S)
- Biochemical studies (Tamaoka et al. 1994; Nilsberth et al. 2001; Sato et al. 2003) (ACMG criterion PS3)
- The same amino acid is mutated to other amino acids by other segregating EOAD pathogenic variants (Chartier-Harlin et al. 1991; Goate et al. 1991; Murrell et al. 2000), and others reviewed in the AD&FTD Mutation Database (Cruts et al. 2012) (ACMG criterion PM5)
- The variant is located in a well-established functional domain at the epsilon cleavage site for gamma secretase (Dimitrov et al. 2013) (and reviewed in (Holtzman et al. 2011)) (ACMG criterion PM1)
- Absent from the gnomAD (Lek et al. 2016) and TOPMed Bravo population databases (NHLBI 2018) (ACMG criterion PM2)
- Predicted damaging by multiple computational methods (CADD (Kircher et al. 2014), PolyPhen-2 (Adzhubei et al. 2010), and SIFT (Ng and Henikoff 2003)) (ACMG criterion PP3).

C9orf72 Expansion Carriers

- Strong segregation with ALS and FTD (DeJesus-Hernandez et al. 2011; Renton et al. 2011) (ACMG criterion PP1S).
- Extensive functional studies support the pathogenicity of this allele (key examples in (Chew et al. 2015; Zhang et al. 2015), and recently reviewed in (Babic Leko et al. 2019; Vatsavayai et al. 2019)) (ACMG criterion PS3).
- *Note on the assumption that C9orf72 expansions will be absent from controls:* two studies have assessed the frequency of C9orf72 expansions in healthy controls, both arriving at a frequency of approximately 0.2% of individuals (Beck et al. 2013; Kaivola et al. 2019) (this would be

equivalent to approximately 1 carrier in our control set of 542 individuals). However, in one of these studies, they also assessed for other neurologic diseases, and found that 4 of 6 individuals with *C9orf72* expansions (out of 3142) had another neurologic disease (Kaivola et al. 2019), leaving only 2 expansion carriers out of 3142 individuals in that study. Therefore, the assumption that no repeat expansion carriers are present in the control set we selected where individuals with a family history of any neurologic disease have been excluded is not unreasonable.

ARSA alleles

In one *C9orf72* expansion carrier, we identified a possibly contributory combination of variants in *ARSA*, associated with recessive metachromatic leukodystrophy (which can include dementia as a symptom): one reported pathogenic variant that may maintain some residual activity (an “R” allele) (NM_000487.5, c.256C>T, p.R86W), and one variant of uncertain significance (VUS) (NM_000487.5, c.585G>T, p.W195C) that may be a pseudo-deficiency allele. Because we did not have phasing data for these two variants and could not follow up with a biochemical test of enzyme activity (the patient died between study enrollment and the observation of the variants in *ARSA*), the specific contribution of these variants is unknown.

- Reported pathogenic variant that may maintain some residual activity (an “R” allele) (NM_000487.5, c.256C>T, p.R86W) (Biffi et al. 2008; Cesani et al. 2016)
- Reported Variant of uncertain significance (VUS) (NM_000487.5, c.585G>T, p.W195C) that may be a pseudo-deficiency allele (Xiong et al. 2015; Cesani et al. 2016; Dehghan Manshadi et al. 2017)
- These alleles were reported together as a VUS, with special emphasis that this combination of alleles may have no or little influence on disease given the presence of a *C9orf72* expansion
- <https://rarediseases.org/rare-diseases/metachromatic-leukodystrophy/>

ABCA7 Loss-of-Function Alleles

- We identified two loss-of-function variants in *ABCA7*: (NM_019112.3, c.2126_2132delAGCAGGG, p.E709Afs*86) and *ABCA7* (NM_019112.3, c.5035G>T, p.E1679*). Loss-of-function variants in *ABCA7* have been solidly associated with AD by several independent case-control studies (Cuyvers et al. 2015; Del-Aguila et al. 2015; Steinberg et al. 2015b; Allen et al. 2017; De Roeck et al. 2017; N'Songo et al. 2017).

APOE ε4 allele

- The APOE ε4 allele is definitively established by a plethora of studies to be associated with AD, with a few key references noted here (Corder et al. 1993; Saunders et al. 1993; Farrer et al. 1997; Lambert et al. 2013; Yu et al. 2014; Qian et al. 2017).

PSEN1 (NM_000021.3, c.103C>T, p.R35W)

- Another VUS in *PSEN1* has been described at Arg35 that does not completely segregate with disease (Rogaeva et al. 2001; Raux et al. 2005; Benitez et al. 2013).

MAPT (NM_005910.5, c.1216C>T, p.R406W)

- Strong segregation with EOAD in multiple studies (Reed et al. 1997; Rademakers et al. 2003; Cruts et al. 2012) (ACMG criterion PP1S).
- Functional studies (Hasegawa et al. 1998; Hong et al. 1998; Krishnamurthy and Johnson 2004; Zhang et al. 2004) (ACMG criterion PS3).
- Predicted damaging by multiple computational methods (CADD (Kircher et al. 2014), PolyPhen-2 (Adzhubei et al. 2010), and SIFT (Ng and Henikoff 2003)) (ACMG criterion PP3).
- Altogether, the presence of two strong criteria and one supporting criterion result in the ACMG-recommended assertion of “pathogenic.”

CSF1R (NM_005211.3, c.2699G>A, p.R900K)

- Critical domain of *CSF1R* where other pathogenic variants also cluster (Rademakers et al. 2011; Stabile et al. 2016) (ACMG criterion PM1)
- Absent from the gnomAD (Lek et al. 2016) and TOPMed Bravo population databases (ACMG criterion PM2)
- This particular variant has been reported before along with segregation data (Kortvelyessy et al. 2015) (ACMG criterion PP1).
- Predicted damaging by multiple computational predictions (CADD, PolyPhen-2, and SIFT) (ACMG criterion PP3).
- Taken together, the presence of two moderate criteria and two supporting criteria result in the ACMG-recommended assertion of “likely pathogenic.”

PLD3 variant (NM_012268.3, c.694G>A, p.V232M)

While the *PLD3* variant described here has been controversial because of replication in some but not all cohorts tested, we considered it a “likely risk variant” based on available evidence (Cruchaga et al. 2014; Cacace et al. 2015; Cruchaga and Goate 2015b; Cruchaga and Goate 2015a; Heilmann et al. 2015; Hooli et al. 2015; Lambert et al. 2015; van der Lee et al. 2015; Engelman et al. 2018). Rare variants are not expected to replicate in all cohorts because of population effects and stochastic sampling.

VUS in APP (NM_000484.3, c.742G>A, p.D248N)

This variant (*APP* (NM_000484.3, c.742G>A, p.D248N)) was returned to the patient as a VUS, but with language indicating that, especially in the presence of the additional variants observed (*APOE* ε4 homozygosity and the *PLD3* V232M variant), it may not contribute much, if at all, to symptoms.

SORL1 M105T

Because this variant lies in a critical functional domain for *SORL1*, the VPS10 domain (Pottier et al. 2012; Caglayan et al. 2014; Louwersheimer et al. 2017), we computational modeled the effect of the

variant. Modelling suggests this is a highly conserved residue (Fig. 3A) where change to a Threonine may create a PLK1 kinase site (Fig. 3B). PLK1 has known roles in the cell cycle, and is aberrantly present in neurons of AD patients but not age-matched controls (Song et al. 2011), leading us to speculate that presence of this variant in SORL1 may lead to faster progression of disease if this kinase phosphorylates this residue, which could disrupt the amyloid- β clearance mechanism of the VPS10 domain (Kitago et al. 2015).

- Studies where *SORL1* M105T would have been observed, but no other carriers of *SORL1* M105T were identified in either cases or controls (Vardarajan et al. 2015; Fernandez et al. 2016; Verheijen et al. 2016; Bellenguez et al. 2017).

TREM2

TREM2 is a well-established risk factor for AD and FTD. References for the specific variants described are as follows:

- *TREM2* (NM_018965.3, c.140G>A, p.R47H) (Guerreiro et al. 2013; Jonsson et al. 2013)
- *TREM2* (NM_018965.3, c.259G>A, p.D87N) (Guerreiro et al. 2013; Cuyvers et al. 2014; Ghani et al. 2015; Jin et al. 2015; Ghani et al. 2016; Piccio et al. 2016)

VPS13C Loss-of-Function Support

- unpublished studies have reported an association between heterozygous loss-of-function variant in *VPS13C* and FTD (Philtjens 2014; Picillo 2018)

Variants of Uncertain Significance and Variants of Research Interest

Variants denoted as “Variants of Uncertain Significance” described in the following section were returned to patients because it would be possible, with limited additional information, for them to become established as associated with the patients phenotype. Variants denoted as of “research interest” in contrast were not returned to patients because it would take a great deal of evidence to establish a definitive link to the patient’s phenotype, but there is limited literature evidence indicating that it is important that we point them out to the field.

573

574 **A possible CADASIL case with two non-Cysteine variants in NOTCH3 (D45H and G52R)**
 575 **spanning C49**

576 A patient with a differential diagnosis of cerebral amyloid angiopathy, leukodystrophy, or
 577 CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and
 578 Leukoencephalopathy) (Joutel et al. 1996) harbored two variants on the same allele in *NOTCH3*
 579 (NM_000435.2, c.133G>C, p.D45H and NM_000435.2, c.154G>A, p.G52R). While these variants do
 580 not induce a typically pathogenic alteration of a Cysteine, they do flank pathogenic variants at residue
 581 Cys49 that have been reported with three different amino acid changes (Clinvar RCV000518559.1,
 582 RCV000710993.1, RCV000518038.1, and (Joutel et al. 1996; Oki et al. 2007; Wang et al. 2011; Meng
 583 et al. 2012)). Both of the variants we observe are in ClinVar as variants of uncertain significance
 584 (RCV000518589.1 and RCV000516491.1). Furthermore, both variants are predicted damaging by
 585 CADD (27.6 and 29.5) and SIFT, and one (D45H) is predicted damaging by PolyPhen-2. We speculate
 586 that, given that these variants fall on the same haplotype, the presence of one or both of these variants
 587 may affect the function of residue Cys49 or other nearby disease-associated Cys residues such as
 588 Cys43 (Clinvar RCV000517549.1) or Cys55 (Clinvar RCV000710994.1 and RCV000516615.1).
 589 Biochemical testing for CADASIL would be informative in this case, and this haplotype was returned as
 590 a variant of uncertain significance with clear language in the report that biochemical testing should be
 591 pursued.

592

593 **A case with a MAPT VUS**

594 A patient with unspecified dementia with an age-of-onset in the late 40s had a VUS returned in
 595 *MAPT* (NM_005910.5, c.1174A>G, p.I392V). Family history information was incomplete for this patient,
 596 precluding knowledge of if a dominant family history was present. The variant had a CADD score of
 597 24.6, was absent from gnomAD (out of 135,743 non-TOPMed individuals), and was present only one
 598 time in TOPMed Bravo (out of 62,784 individuals). The closest pathogenic variants are R406W (already
 599 described) and G389R (Murrell et al. 1999; Ghetti et al. 2000; Pickering-Brown et al. 2000;
 600 Bermingham et al. 2008; Rossi et al. 2008). Of note, these established pathogenic variants are present

four and three times in gnomAD, respectively, indicating that the rarity of the VUS observed here justifies return to the patient as a VUS. The uncertainty around this variant was emphasized in the letter to the patient.

A case with APOE ε4 Heterozygosity, ADAM10 I120T, and TTC3 V1893M

A patient with corticobasal syndrome with onset in the early 50s and positive amyloid PET was found to harbor two variants of research interest, but that did not reach the level of evidence needed for return of the variants as a VUS. The variants were in *ADAM10* (NM_001110.3, c.359T>C, p.I120T) and *TTC3* (NM_001001894.2, c.5557G>A, p.V1853M). The *ADAM10* variant had a borderline CADD score of 14.3 and was not predicted damaging by PolyPhen-2 or SIFT. Furthermore, the variant was observed in gnomAD 12 times. *ADAM10* has been proposed as a candidate gene for AD in prior studies (Kim et al. 2009) including two variants in the same domain as the variant identified here, the prodomain (Suh et al. 2013). Furthermore, variation in *ADAM10* recently reached genome-wide significance for association with AD by GWAS (Marioni et al. 2018; Kunkle et al. 2019). However, we have chosen to not return this variant in the absence of more information about effect size or segregation. The *TTC3* variant also had a borderline CADD score (14.6) and was not predicted damaging by PolyPhen-2 or SIFT. However, this variant was not observed in gnomAD or TOPMed Bravo. A different *TTC3* variant (NM_001001894.2, c.3113C>G, p.S1038C) has been reported to segregate with late-onset AD in one family (Kohli et al. 2016). However, since we lacked segregation data for the variant we observed, we did not have enough evidence to consider the *TTC3* variant as more than a variant of research interest, and thus did not return the variant to the patient.

A case with APOE ε4 Heterozygosity, SORL1 R416Q, and MME Y414C

A case with mild dementia of uncertain etiology and symptoms consistent with neuropathy with onset in the mid 50s had one *APOE* ε4 allele along with variants in *SORL1* (NM_003105.5, c.1247G>A, p.R416Q) and *MME* (NM_007289.2, c.1241A>G, p.Y414C). This *SORL1* variant has a CADD score of 34 and is also predicted damaging by PolyPhen-2 and SIFT. A link between *MME* and neurodegeneration, including AD and neuropathy, has previously been proposed (Rey-Salgueiro et al.

2009; Auer-Grumbach et al. 2016; Depondt et al. 2016), but there was insufficient evidence for this particular variant in *MME* or for the *SORL1* variant to justify return to the patient.

A case with TM2D3 P69L and TNK1 H131Q

A patient with mild dementia due to either AD or bvFTD with onset in the mid 50s had variants in *TM2D3* (NM_078474.2, c.206C>T, p.P69L) and *TNK1* (NM_001251902.1, c.393C>G, p.H131Q). A different variant in *TM2D3* has been nominated as AD-associated from an Icelandic cohort (Jakobsdottir et al. 2016). Other variants in *TNK1* have been nominated as AD-associated from analysis of Alzheimer's Disease Sequencing Project data (He et al. 2017). While neither of these variants had sufficient evidence for return as risk variants, our observation of these variants in this cohort adds evidence for the possible contribution of variants in these genes to disease.

Secondary Finding

One patient harbored a secondary pathogenic variant in *KCNQ1* (NM_000218.2, c.1552C>T, R518*), associated with cardiac arrhythmias. This is a known founder effect variant from the Swedish population that responds well to beta blockers (Winbo et al. 2014). The variant is a null variant in a gene where loss-of-function is a known mechanism of disease (ACMG criterion PVS1) and is enriched in cases vs. controls with an odds ratio >5 (ACMG criterion PS4) (Kapplinger et al. 2009). Furthermore, the variant's effect is supported by well-established functional studies (Harmer et al. 2014) (ACMG criterion PS3). Taken together, the presence of one very strong criterion and two strong criteria result in the ACMG-recommended assertion of "pathogenic." Consistent with the study consent and protocol, presence of this variant was reported to the patient.

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FIGURE LEGENDS

Figure 1. Summary of genomic analysis results for 32 patients with early-onset or familial

dementia. Pathogenic variants were observed in APP (x2), C9orf72 (x3), and MAPT (x3). A likely pathogenic variant was observed in CSF1R. Four patients were APOE ϵ 4 homozygous, with three of these patients also harboring additional risk variants in GBA, PLD3, and TREM2. Three patients were APOE ϵ 4 heterozygous and had additional risk variants in AKAP9, SORL1, and TREM2. Two patients had variants of uncertain significance (VUS) in MAPT and NOTCH3. For six patients, the only returnable finding was APOE ϵ 4 heterozygosity. Eight patients had no returnable findings.

Figure 2. Neuroimaging findings in a CSF1R variant carrier. (A,B) Frontal-predominant, mildly asymmetric (R>L) white matter hyperintensities on axial FLAIR images. **(C,D)** Global cerebral atrophy on coronal and axial MPRAGE images. Radiological orientation with patient's R side displayed on L.

Figure 3. Molecular modeling of the effect of the M105T variant on SORL1. (A) Conservation analysis of the SORL1 gene sequence was performed across open reading frame sequences of 135 species. Scores at each codon were assessed with 100% conservation receiving a score of 1, with addition of a score for codon selection (score of 0 if dN-dS of site is below mean, 0.25 for sites with values above the mean to one standard deviation above the mean, 0.5 for sites greater than one standard deviation but below two standard deviations, one for sites greater than two standard deviations). A score of two is maximal, suggesting an amino acid that is 100% conserved with codon wobble indicative of a high selection rate at the position. The values were then placed on a 21-codon sliding window (combining values for 10 codons before and after each position) to identify conserved motifs within the gene. **(B)** Model of SORL1 protein (assessed with YASARA2). Colors are based on 135 species alignments fed into ConSurf such that colors indicate: gray=not conserved, yellow=conserved hydrophobic, red=conserved polar acidic, blue=conserved polar basic, green=conserved hydrophilic. Note that the M105T variant leads to a predicted gain of a PLK1 kinase target site in SORL1.

Figure 4. Multiple variants in neurodegeneration-associated genes are often observed in early-onset dementia, with a critical role for rare variants acting in combination with APOE ε4. Note: for all panels, ε4/ε* indicates either ε4/ε3 or ε4/ε2 (mostly ε4/ε3). Also for all panels, cases N=31 (32 probands excluding 1 sibling from an affected sibling pair) and controls N=542. **(A)** Qualifying candidate alleles associated with neurodegeneration (see text for criteria) are highly enriched in cases ($p=9.2 \times 10^{-12}$ by exact conditional Cochran-Armitage trend test). **(B)** Presence of APOE ε4 alone, in the absence of any other qualifying variants, is not enriched in cases ($p=0.57$ by exact conditional Cochran-Armitage trend test). **(C)** Presence of APOE ε4 along with at least one qualifying rare variant (including Mendelian variants) is highly enriched in cases ($p=1.0 \times 10^{-9}$ by exact conditional Cochran-Armitage trend test). **(D)** Presence of APOE ε4 along with at least one qualifying rare variant (excluding Mendelian variants) is highly enriched in cases ($p=1.4 \times 10^{-6}$ by exact conditional Cochran-Armitage trend test). The odds ratio for Presence of one APOE ε4 allele along with one qualifying rare variant vs. controls is 5.5 ($p=0.01$ by Fisher's exact test, 95% CI 1.2–19.3). The odds ratio for Presence of two APOE ε4 alleles along with one qualifying rare variant vs. controls is 39.1 ($p=9.8 \times 10^{-5}$ by Fisher's exact test, 95% CI 5.3–447.5).

Table 1: Variant Table. Note that many individuals had multiple candidate contributory variants, which is not captured when considering variants individually. For an expanded table that indicates multiple candidate variants, see **Supplemental Table 1**.

Supplemental Table 1: Phenotype and variant table. Prior clinical diagnosis category, age of onset range, family history score, **Figure 1** category, and variant information listed in **Table 1** for each proband are listed along with information on which variants were returned to patients and which did not have sufficient evidence for return but are of research interest. Note that some detailed information such as sex, age of onset to the year, self-reported ethnicity, and detailed phenotype and family history information has been excluded to protect the identity of participants but is available along with raw data via controlled access to qualified researchers.

Figure 1:

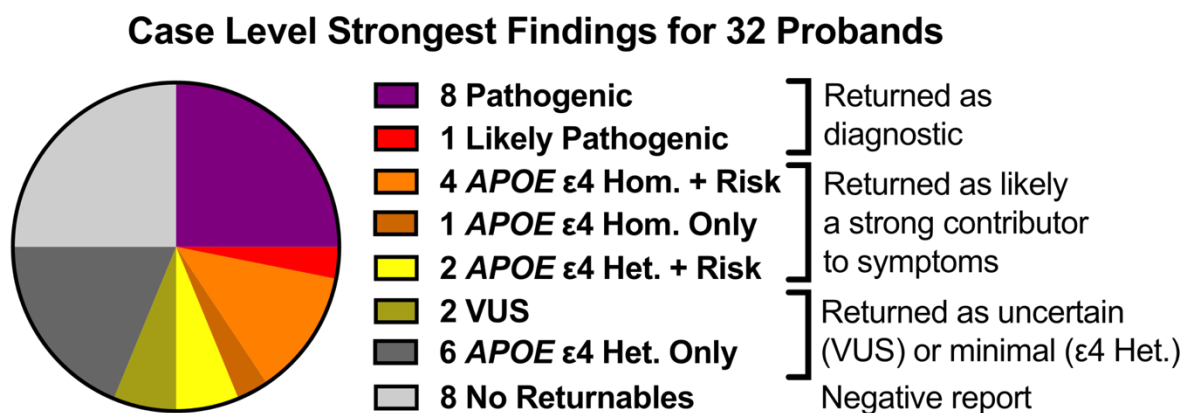


Figure 2:

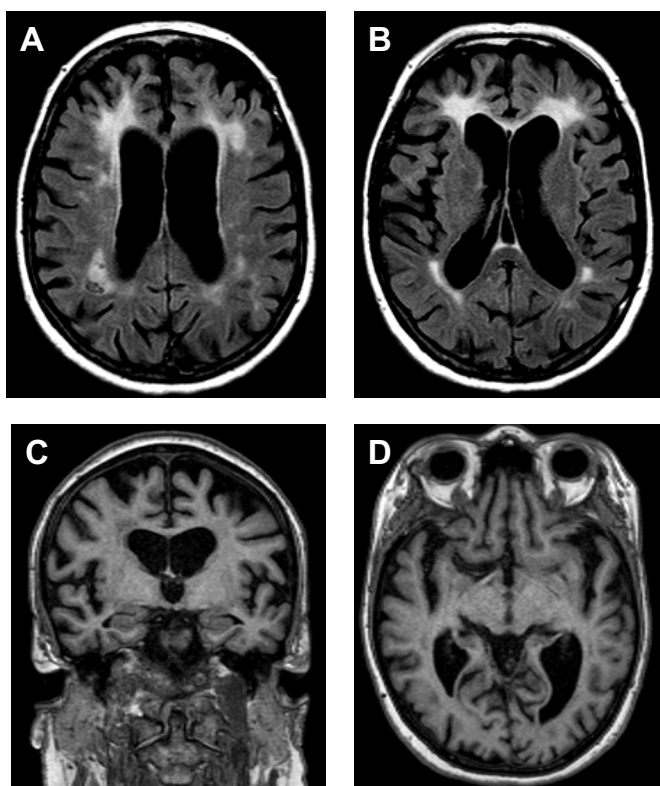


Figure 3:

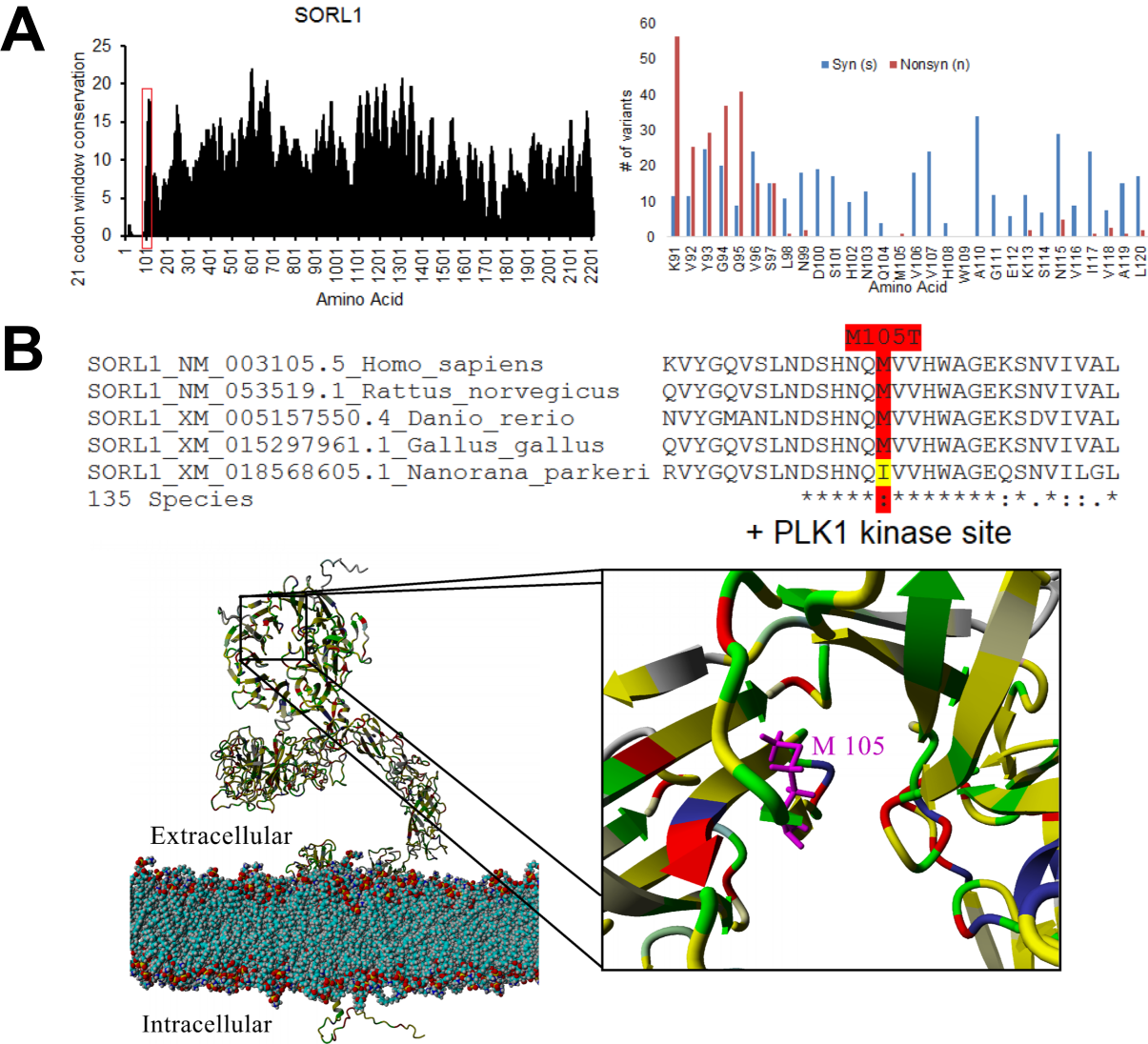
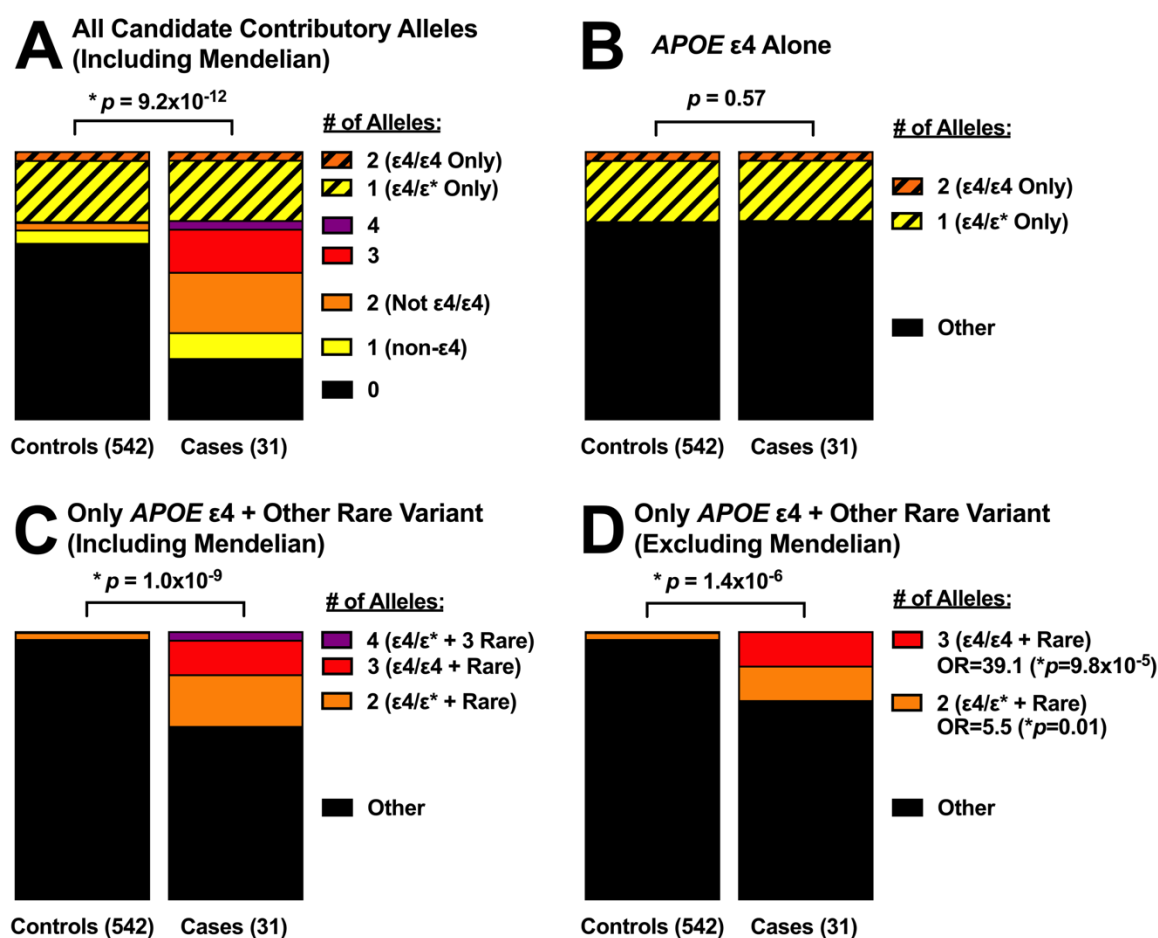


Figure 4:



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Table 1:

Gene	Chrom.	HGVS DNA	HGVS Protein	Variant Type	Predicted Effect	dbSNP ID	Genotype
<i>APP</i>	21	NM_000484.3:c.2149G>T	V717F	SNV	Missense	rs63750264	Heterozygous
<i>C9orf72</i>	9	NM_001256054.1:c.-45+163_-45+168GGGGCC[(24_?)]	NA	Insertion	Repeat Expansion	rs143561967	Heterozygous
<i>ABCA7</i>	19	NM_019112.3:c.5035G>T	E1679*	SNV	Stop Gained	rs770510230	Heterozygous
<i>APOE</i>	19	NM_000041.3:c.388T>C	C130R	SNV	Missense	rs429358	Het & Hom
<i>APOE</i>	19	NM_000041.3:c.526C>T	R176C	SNV	Missense	rs7412	Ref. (w/ Above Alt = ε4)
<i>PSEN1</i>	14	NM_000021.3:c.103C>T	R35W	SNV	Missense	rs746691776	Heterozygous
<i>ABCA7</i>	19	NM_019112.3:c.2126_2132del AGCAGGG	E709Afs*86	Deletion	Frameshift	rs547447016	Heterozygous
<i>ARSA</i>	22	NM_000487.5:c.256C>T	R86W	SNV	Missense	rs199476352	Compound Het
<i>ARSA</i>	22	NM_000487.5:c.585G>T	W195C	SNV	Missense	rs6151415	Compound Het
<i>MAPT</i>	17	NM_005910.5:c.1216C>T	R406W	SNV	Missense	rs63750424	Heterozygous
<i>APP</i>	21	NM_000484.3:c.1090C>T	L364F	SNV	Missense	rs749453173	Heterozygous
<i>GRID2IP</i>	7	NM_001145118.1:c.429+2T>G	NA	SNV	Splice	rs1413118387	Heterozygous
<i>CSF1R</i>	5	NM_005211.3:c.2699G>A	R900K	SNV	Missense	NA (private)	Heterozygous
<i>PLD3</i>	19	NM_012268.3:c.694G>A	V232M	SNV	Missense	rs145999145	Heterozygous
<i>APP</i>	21	NM_000484.3:c.742G>A	D248N	SNV	Missense	rs200103591	Heterozygous
<i>ABI3</i>	17	NM_016428.2:c.290T>A	V97E	SNV	Missense	NA (private)	Heterozygous
<i>SORL1</i>	11	NM_003105.5:c.314T>C	M105T	SNV	Missense	rs982581946	Heterozygous
<i>TREM2</i>	6	NM_018965.3:c.140G>A	R47H	SNV	Missense	rs75932628	Heterozygous
<i>TREM2</i>	6	NM_018965.3:c.259G>A	D87N	SNV	Missense	rs142232675	Heterozygous
<i>AKAP9</i>	7	NM_005751.4:c.7638A>G	I2546M	SNV	Missense	rs144662445	Heterozygous
<i>GBA</i>	1	NM_000157.3:c.1448T>C	L483P	SNV	Missense	rs421016	Heterozygous
<i>VPS13C</i>	15	NM_020821.2:c.10954C>T	R3652*	SNV	Stop Gained	rs138846118	Heterozygous
<i>VPS13C</i>	15	NM_020821.2:c.1988delC	T663Nfs*2	Deletion	Frameshift	rs1019238429	Heterozygous
<i>PLCD1</i>	3	NM_006225.3:c.631C>T	R211W	SNV	Missense	rs752156828	Heterozygous
<i>NOTCH3</i>	19	NM_000435.2:c.133G>C	D45H	SNV	Missense	rs142031490	Compound Het
<i>NOTCH3</i>	19	NM_000435.2:c.154G>A	G52R	SNV	Missense	rs148166997	Compound Het
<i>MAPT</i>	17	NM_005910.5:c.1174A>G	I392V	SNV	Missense	rs991713081	Heterozygous
<i>ADAM10</i>	15	NM_001110.3:c.359T>C	I120T	SNV	Missense	rs144890810	Heterozygous
<i>TTC3</i>	21	NM_001320703.1:c.5677G>A	V1893M	SNV	Missense	NA (private)	Heterozygous
<i>SORL1</i>	11	NM_003105.5:c.1247G>A	R416Q	SNV	Missense	rs377550239	Heterozygous
<i>MME</i>	3	NM_007289.2:c.1241A>G	Y414C	SNV	Missense	rs202095767	Heterozygous
<i>TM2D3</i>	15	NM_078474.2:c.206C>T	P69L	SNV	Missense	rs140152371	Heterozygous
<i>TNK1</i>	17	NM_001251902.1:c.393C>G	H131Q	SNV	Missense	rs767381816	Heterozygous
<i>KCNQ1</i>	11	NM_000218.2:c.1552C>T	R518*	SNV	Stop Gained	rs17215500	Heterozygous

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