Genetic testing in dementia – how to do it

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Abstract

There is growing public awareness and concern regarding dementia risk. In addition, genetic testing is increasingly accessible and now at the point of being integrated into routine clinical practice. As a result, there is a pressing need for treating clinicians to have the appropriate knowledge base to request and consent for diagnostic genetic testing in cognitive clinics. We outline our approach to genetic testing in patients with Alzheimer's disease, frontotemporal dementia , dementia with Lewy bodies and vascular cognitive impairment. We discuss when to consider testing, the consenting process, and the interpretation and communication of genetic test results.

Introduction

The approval of disease-modifying-therapies for Alzheimer's disease (AD) heralds a new era of dementia care and has led to growing public awareness and concern regarding dementia

risk. A small, but important, proportion of the most commonly diagnosed dementias are due to monogenic disorders associated with an autosomal dominant inheritance pattern: approximately one third of frontotemporal dementia (FTD) , <1% of Alzheimer's disease and an even lower proportion of those with vascular dementia or dementia with Lewy bodies (DLB)[1]. Carriers of pathogenic mutations are often unaware of their inheritance risk as preceding generations could not access genetic testing, or due to incomplete penetrance and variable expressivity.

A genetic diagnosis has important implications for patients—a change in management occurs in 50–70% of adults receiving a genetic diagnosis[2,3], usually centring around more personalised care with referrals to specialist services and/or improved understanding of prognosis. Identification of a pathogenic mutation can have diagnostic value, confirming the clinical phenotype and thus avoiding need for further investigations (e.g. serial neuropsychometry, longitudinal MRI and/or functional imaging, lumbar puncture). It can open up avenues to research participation, as well as facilitating access to tailored support groups[2]. A genetic diagnosis also has implications for family members—testing improves understanding of risk, and can facilitate access to genetic counselling, presymptomatic testing and reproductive options.

Genetic testing practices differ within and between healthcare systems. In the UK and Ireland, there is a long history of neurologists performing single gene diagnostic testing in neurodegenerative conditions such as Huntington's disease. Neurologists are now also gaining increasing experience in requesting and interpreting broader genetic panels, with neurology contributing the greatest number of cases of any medical speciality to the UK's 100,000 Genomes Project[4]. However there are inter-regional differences in detecting genetic dementia syndromes; detection rates of familial Alzheimer's disease have previously been found to vary by up to 70% across the UK[5]. As we enter an era of genomic medicine, with a significant increase in demand for clinical genetic services, there is an increasing responsibility for clinicians not primarily trained in genetics to acquire the appropriate knowledge base to request genetic testing in dementia syndromes competently [6,7]. Therefore, we discuss an approach to diagnostic genetic testing in the most commonly

diagnosed dementias and outline some general principles for when to consider a genetic diagnosis and what tests to send, as well as for the consenting and result-giving process.

Who to test

Diagnostic genetic testing should only be pursued in patients who are symptomatic and likely to benefit. The decision to offer testing will be influenced by the age at onset, family history and clinical phenotype[8]. It is crucial to clarify the exact age at onset and to obtain a detailed multi-generation family history (for further guidance see "How to take a family history"); however, a negative family history, or onset after the age of 65 years, does not preclude a genetic diagnosis[9]. Diagnostic yield varies depending on clinical phenotype, and therefore we outline separately in individual textboxes our approach to testing in Alzheimer's disease, FTD, dementia with Lewy bodies and vascular cognitive impairment.

Textbox

How to take a family history

It is essential to obtain a detailed multi-generation family history, which can inform a Goldman score (Figure 1)[9]. Any neurological and/or psychiatric presentation should be explored, specifically recording initial phenotype, progression and age at onset, and death. Treat diagnostic labels with caution as misdiagnosis of dementia was frequent in previous generations. Unclear psychiatric histories should not be taken at face value and instead characterised in as much detail as possible. If relatives have lost contact, it is important to explore why, as this may be attributable to the onset of a neurodegenerative disease. The occurrence of seizures, parkinsonism and motor neurone disease should always be documented. A negative history does not preclude a genetic diagnosis, as there is the possibility of non-paternity and family histories can be incomplete or censored (i.e. unrelated early deaths). Mutations can have incomplete penetrance, especially if associated with older age at onset and variability in onset, or occur *de-novo*.

Textbox:
Alzheimer's Disease

Familial Alzheimer's disease is an autosomal dominant condition caused by pathogenic mutations in amyloid precursor protein(*APP)*, presenilin 1/2(*PSEN1/2)*, and *APP* duplications. The estimated prevalence is 5.3/100,000 persons aged <60 years [10], accounting for up to 5% of early-onset Alzheimer's disease (onset <65)[8]. Younger age at onset and family history predict risk; >85% of those with onset before 60 and a three-generation family history carry a pathogenic mutation[1]. Family history and/or early onset is not mandatory: mutations can have incomplete penetrance, especially if onset is after 65, and *de-novo* mutations can account for 10% of apparently sporadic cases with onset before 51[11].

Familial Alzheimer's disease is most commonly caused by mutations in *PSEN1(*30-70%) followed by *APP(*10-15%), with *PSEN2* being the least common. An array of genetic conditions can mimic familial Alzheimer's disease (Table 1)[12]. *PSEN1* carriers have an earlier onset(typical range:30-60years) compared to *APP* carriers (range: 40-60 years), while *PSEN2* have later and more variable onset (typically 50-65years); age at onset is reasonably consistent within families and individual variants, but can have some variability[13,14].

As with sporadic Alzheimer's disease, amnestic presentations occur most commonly: 97% of *APP* and 84% of *PSEN1*[14] in a case series of families from the UK and Ireland. There may be atypical presentations, including behavioural–dysexecutive and language-led syndromes [14,15]. However posterior cortical atrophy presentations can occur rarely. Additional neurological signs may indicate familial Alzheimer's disease*:* pyramidal dysfunction occurs in 20–25% of *PSEN1* cases and can appear early in the disease course[14,15]. Myoclonus develops in 30–50% of familial Alzheimer's disease patients and can be a harbinger of future seizures (frequency≈25%)[14,16]. Seizures can be an early feature, occasionally predating cognitive decline[17]. Atrophy occurs in a similar pattern to sporadic Alzheimer's disease. White matter hyperintensities can be prominent, especially in *PSEN1* post-codon200 carriers[18,19]. Additionally, a proportion of *APP* carriers (*APP* duplications or mutations within the amyloid-beta coding domain) may present with intracerebral haemorrhages secondary to cerebral amyloid angiopathy[20].

SORL1 was initially considered an Alzheimer's disease risk gene. However, Alzheimer's disease risk varies depending on mutation type and site: protein-truncating variants

increase risk of early-onset Alzheimer's disease by 36-fold, while certain missense variants(high-priority variants) lead to a 10-fold increase in this risk[21]. This has led to calls for clinicians to consider certain *SORL1* variants when screening for familial Alzheimer's disease. In cases where a high risk *SORL1* variant is reported, segregation analyses should be considered.

It is our practice to discuss the possibility of genetic testing with individuals with Alzheimer's disease symptom onset before the age of 60 or a strong family history (Goldman Score 1-2-scoring outlined in Figure 1), unless there is a valid reason not to. A case-by-case approach is needed for cases with a less clear family history (Goldman score 3) or onset between 60 and 65 years. Factors that influence testing decisions include censored/limited family history, and implications for family members – threshold for testing will be lower in those where a genetic diagnosis would inform family planning or other decisions in future generations.

The apolipoprotein E ε4 (*APOE4*) allele, which occurs in about 20% of the general population, is the most important genetic susceptibility risk factor for Alzheimer's disease, with a recent a study showing near-full penetrance of Alzheimer's disease biology in *APOE4* homozygotes by age 65[22,23]. However, carriage of *APOE4* alone is not routinely considered sufficient to cause symptomatic Alzheimer's disease: 50% of homozygotes and 20% of heterozygotes develop symptomatic Alzheimer's disease before age 85[24]. Risk varies across ethnic groups with carriage of a single *APOE4* allele having a reported odds ratio 2–4 times that of non-carriers, while homozygosity increases odds ratio to 4–13[25]. *APOE4* homozygosity is associated with earlier onset and can mimic autosomal dominant inheritance, particularly if both parents are APOE4 homozygous as their homozygous offspring are at high risk of developing Alzheimer's disease. A history of consanguinity and/or greater than expected variability in age at onset can sometimes indicate *APOE4* carriage. Currently there is no clinical role for *APOE* testing in the UK and Ireland; testing is however available through some direct-to-consumer companies. The clinical situation is likely to change as disease-modifying therapies enter use: *APOE4* haplotype is a contributor to risk of amyloid-related imaging abnormalities and therefore genotyping can inform patient consenting and may be recommended, or potentially required, to ensure appropriate patient selection for therapies[26].

Textbox

- **Frontotemporal Dementia**

Frontotemporal dementia (FTD) is an umbrella term for an array of clinical and pathological entities. Approximately one third of cases are familial, with heritability varying across phenotype: behavioural-variant FTD is most frequently familial; however language-led phenotypes, particularly mixed variants of primary progressive aphasia, as well as FTD overlap syndromes, especially FTD-motor neurone disease presentations, can also show heritability[27]. Families with multigenerational inheritance and earlier onset are more likely to be genetic: >90% of patients with a strong autosomal dominant family history carry a relevant pathogenic mutation[1].

Three genes account for over 90% of familial FTD: expansions in chromosome 9 open reading frame 72(*C9ORF72),* followed by variants in progranulin (*GRN*) and microtubule-associated protein tau(*MAPT*)[28]. The most common FTD phenotype across these three genes is behavioural variant FTD but phenotypic heterogeneity occurs even within the same gene, especially for *C9ORF72*(see Table 2). Mutations in other genes, such as *TBK1, VCP, TARDBP, FUS, CHMP2B, SQSTM1,* and *CHCHD10,* account for a small percentage of genetic FTD with frequency varying across geographic regions, depending on the impact of founder mutations[28].

Age at onset varies, especially for *GRN* and *C9ORF72* carriers, but at a group level, is earlier in *MAPT* (average=50y, range 20s–80s) compared with *GRN* (average=61y, range 20s–90s) and *C9orf72* (average=58y, range 20s–90s) cases[29]. There can be reduced penetrance of both *C9ORF72* and *GRN* mutations, however pathogenic *MAPT* mutations are almost 100% penetrant and have a reasonably consistent age at onset within families[29].

We recommend offering genetic testing to those with behavioural variant FTD or FTD-motor neurone disease, even in the absence of a family history. In the other FTD phenotypes, we perform genetic testing on a patient-by-patient basis, but typically only in those with a strong family history, as the likelihood of finding a pathogenic mutation in the absence of a family history is low – see Figure 1. An exception is atypical primary progressive aphasia

syndromes that do not fit criteria for any of the three canonical subtypes as this raises the possibility of a *GRN* mutation[30].

Textbox

- **Dementia with Lewy Bodies**

Dementia with Lewy bodies is typically a sporadic disease with only a small number of cases being attributed to deterministic mutations[31]. Familial presentations are often atypical and show significant clinical heterogeneity—even within families—with described phenotypes including dementia with Lewy bodies, Parkinson's disease, Parkinson's disease dementia, multiple system atrophy and FTD [31]. *SNCA* (either multiplications or missense mutations) is the most common gene in familial dementia with Lewy bodies cases and has incomplete penetrance. There are also susceptibility genes (*APOE4* carriage*,* heterozygous variants in *GBA)* that predispose individuals to developing dementia with Lewy bodies, but do not guarantee disease onset[31]. Additionally, other autosomal dominant mutations (*PSEN2, CHMP2B, EIFG1, CSF1R, GIFYF2, SQSTM1, PARK2* and *C9ORF72)* can serve as mimics[31]. We recommend only offering genetic testing in patients with dementia with Lewy bodies where there is a compelling multigenerational history of parkinsonian and/or cognitive disorders.

Textbox

- **Inherited white matter disorders and monogenic forms of cerebral small vessel disease**

Inherited white matter disorders are a large and heterogeneous group comprising the leukodystrophies and genetic leukoencephalopathies. The most frequent clinical presentation of inherited white matter disorders is a variable combination of cognitive impairment, neuropsychiatric changes and movement disorders, usually accompanied by upper motor neurone signs and confluent T2W/FLAIR signal abnormality in brain white matter. A description of the full spectrum of adult-onset inherited white matter disorders is beyond the scope of this review, but important disorders to consider include *CSF1R*-related leukoencephalopathy and Alexander disease, as there are clinical trials in process for early symptomatic patients, as well as the vasculopathies, or monogenic forms of cerebral small vessel disease. These include cerebral autosomal dominant arteriopathy with subcortical

infarcts and leukoencephalopathy (CADASIL) as well as mutations in *HTRA1,* Fabry disease, *COL4A*-related disorders and several other rare disorders, listed in Table 3.

An inherited disorder should be suspected in patients who are young (e.g. less than 50 years of age), without typical vascular risk factors and/or with a suggestive family history[32]. Further information on the diagnostic approach to inherited white matter disorders including monogenic forms of cerebral small vessel disease can be found elsewhere (Lynch et al and Williams *et al*.)[33,34].

When to test

Pursuing genomic testing presents unique challenges, as these tests provide data that have implications not only for the patient but also for their wider family. It is important to explore with patients and their relative(s) their understanding of what a genetic condition is, and to allocate dedicated time to the consenting process (see below). Many patients, especially those with a strong family history, report a concern about inheritance risk and are keen to discuss genetic testing once a neurodegenerative diagnosis is established. For others, for example if there is a censored family history, the concept of heritability may be unexpected. Patients should be offered the opportunity to discuss genetic testing with family members and the option of a second appointment, if needed, to complete pre-test discussions (see Figure 2).

If there are complex diagnostic or psychosocial/familial considerations, then neurologists should consider onward referral to Clinical Genetics services for formal counselling. If there is no immediate plan to proceed to genetic testing, clinicians should discuss the option of DNA storage for future testing. This can be particularly valuable if there are at-risk children who may develop concerns about their own risk.

Genetic testing is performed by neurologists only in those who are symptomatic. Unaffected relatives at risk of a genetic dementia are instead referred to clinical genetics services for appropriate presymptomatic genetic counselling. Individuals without a confirmed mutation in their family are unlikely to have access to presymptomatic genetic testing, as this is not usually possible in the absence of an established genetic diagnosis in an

affected family member, highlighting the the importance of testing or storing sample in the proband.

How to consent

The goal of obtaining informed consent for genetic investigations is to ensure that patients and their family members understand the benefits, risks, and limitations of genetic testing. Consenting should ideally involve a family member. Clinicians should discuss the 50% inheritance risk for first-degree relatives, should an autosomal dominant mutation be detected, as well as how this information would be shared in the family.

The benefits of genetic testing can include possible diagnostic clarity, which can be particularly valuable in cases of a long diagnostic odyssey. Identification of mutations can give a sense of control over a family illness. A genetic diagnosis can lead to targeted treatments and dedicated research opportunities, as well as facilitating access to predictive testing for family members through clinical genetics services. A confirmed mutation in a first-degree relative opens up specialised reproductive options including access to prenatal testing and/or pre-implantation genetic testing; this procedure allows those at risk, who may not need to find out their own mutation status, to have unaffected children (more detail on this process can be found at https://www.hfea.gov.uk/treatments/embryo-testing-and-treatments-for-disease/pre-implantation-genetic-testing-for-monogenic-disorders-pgt-m-and-pre-implantation-genetic-testing-for-chromosomal-structural-rearrangements-pgt-sr/). Individuals may benefit from the peer support of connecting with other families affected by similar rare genetic forms of dementia[35]. Family members can also participate in research studies including clinical trials and may in the future have opportunities to access presymptomatic therapies should they become available.

Risks include the possibility of finding one or more variants of uncertain significance. A variant of uncertain significance is a change in the genetic sequence where the association with disease risk is unclear i.e. the variant does not fulfil the classification criteria for being either benign or pathogenic and/or the evidence for either categorisation is conflicting[36]. Identifying a variant of uncertain significance may leave patients and families with the

troubling knowledge that a genetic finding has been made but its implications in terms of risk and pathogenicity are unclear.

The consenting process also needs to address broader risks and impact on family members. Genetic test results enter a symptomatic individual's medical records, as well becoming part of the wider family history, which must be disclosed on insurance applications. The psychosocial burden of living at risk of a hereditary dementia can be substantial, including an increased likelihood of developing depressive symptoms, hopelessness, suicidal ideation and negatively impacting on long-term relationship planning[37,38].

The limitations of genetic testing should be discussed: specifically, testing does not guarantee the identification of a pathogenic mutation, even when the family history is strong. New genes may be discovered in the future and a test may not identify all possible mutations.

Obtaining consent can be difficult in patients with cognitive impairment and should be facilitated as much as possible by simplifying information, providing visual aids and including a trusted individual in the discussion[39]. The decision to test patients who lack capacity should be based on their best interests, i.e. is this a test that will inform their diagnosis, treatment or management[40]. A best-interests decision should also incorporate the person's past wishes in relation to genetic testing and the opinions of family members and carers interested in the person's welfare[40]. At times the primary motivation for genetic testing may be to inform risk in other family members—there is legal precedent in the UK that this may still be in the best interests of adults lacking capacity—but such decisions should be made in consultation with family members and a person's power of attorney[40]. The option of DNA storage for future testing should be discussed if uncertainty remains.

What tests to send

The advent of next-generation sequencing with whole-exome sequencing and whole-genome sequencing has transformed genetic testing. This technology facilitates mass sequencing of a selection of genes(panels), the exome (all the protein-encoding sequences)

or the whole genome (introns and exons). These tests detect missense mutations and small insertions/deletions, but detection of larger deletions/insertions, copy number variants, and tandem repeat can be hampered by read length. However, with advanced bioinformatics, whole-genome sequencing can detect some pathological repeat expansions and/or small copy number variants that can then be confirmed using secondary testing, such as fragment analysis or Sanger sequencing[36].

Many next-generation squencing panels, depending on testing methods employed, cannot reliably detect hexanucleotide repeat expansions in *C9orf72,* octapeptide repeat expansions in the prion protein gene *(PRNP) (*a mimic of familial Alzheimer's disease - Table 1*),* nor *APP* or *SNCA* multiplications. One should always check that repeat expansions and/or gene duplications can be identified by the genetic test being performed if these conditions are in the differential, or this could lead to a false negative [36,38]. In particular it is important to test for *APP* duplications in those with a suggestive phenotype (young-onset Alzheimer's disease with positive family history, cerebral amyloid angiopathy and/or prominent white matter change and seizures). Given the heterogeneity and pleiotropy of genetic dementias, we currently perform whole-genome sequencing with a dementia (neurodegeneration) panel including analysis of relevant repeat expansions including *HTT,C9orf72* and *PRNP* genes and, if appropriate, relavant multiplications. As technology and pricing evolves, first-line whole-genome sequencing is increasingly feasible, although still expensive in many countries and bioinformatically challenging. Clinicians should consider a low threshold for DNA storage in all patients with early or familial dementia, especially if there is a high index of suspicion, but where they either do not meet testing criteria or decline testing.

Approaches to genetic testing can vary from region to region, as well as from country to country. In the UK an annually updated National Genomic Test Directory (https://www.england.nhs.uk/genomics/the-national-genomic-tes t-directory), which lists the available tests, their indications, and the testing methods used, helps to standardise the approach to genetic testing across the NHS in England.

How to communicate results

Patients and their families should receive genetic test results (positive or negative) in a way that is sensitive to the context and implications for that individual and their wider family. It is important to choose wording carefully: for instance describing a result as “positive” risks being misunderstood. Figure 3 outlines considerations for giving either a positive or negative genetic result.

Following a positive genetic test, the patient and their family member(s) need to be counselled on the inheritance pattern, prognosis and availability of clinical interventions. Practice may vary within and between healthcare systems; however it is usually reasonable for a treating clinician with the appropriate knowledge base to provide this information and counselling. Patients should be provided with support materials as well as being signposted to relevant support groups and research opportunities. The Rare Dementia Support website is a useful resource with dedicated information on familial Alzheimer’s disease and familial FTD. Onward referral to a specialist clinic, where available, should be considered, while counselling of the wider family, and consideration of predictive/prenatal testing, can only be carried out in specialist genetic clinics.

Following a negative test, it is important to discuss the limitations of genetic testing: specifically, a negative result does not guarantee that the disorder is not inherited. In cases where is there a high index of suspicion that the condition is genetic one should consider onward contact with a research group.

Challenges

A growing challenge facing clinicians is to determine the significance of a variant of uncertain significance. It is our practice to approach this question in multi-disciplinary meetings involving clinicians and geneticists who together evaluate (1) the clinical phenotype, (2) segregation of the mutation with the disease (not always possible in older-onset cases) and (3) the molecular properties and frequency of the mutation in healthy controls, and then to use this information, in combination with the American College of

Medical Genetics and Genomics guidelines, to reach a consensus decision[41]. In cases where a variant has left ongoing uncertainty, post-mortem brain donation should be discussed as this can provide diagnostic clarity for family members[42].

The future

As we enter an era of disease-modifying therapies and personalised medicine, we need to address discrepancies in genetic testing practices across different disciplines seeing patients with dementia, and inequity of access to specialist diagnostic services. Additionally there will be significant challenges in managing genetic testing and addressing results, especially as these tests becomes more accessible on samples such as saliva, and through direct-to-consumer genetic testing companies where there is limited or no prior counselling or post-test support. It is critically important that families with a pathogenic mutation, whether or not this is identified through approved clinically-initiated testing, have access to targeted support, research opportunities and, should they become available, disease-modifying therapies.

Key points

- All patients with dementia should have a detailed multi-generation family history, including (for all affected relatives) age at symptom onset, details of phenotype and age and cause of death.
- Advantages of a confirmed genetic diagnosis include diagnostic clarity, access to speciality clinics, targeted treatments and dedicated research opportunities, as well as informing reproductive planning in family members.
- Consenting should include discussion on the possibility of unclear and/or ‘unexpected’ results.
- DNA storage should be discussed in cases where there is uncertainty about proceeding to genetic testing.

Tables

Table 1

Genetic mimics of familial Alzheimer's disease

Gene/ Genetic group	Associated features
MAPT – particularly **Intron 10+16, R406W, P301L**	There may be early amnestic features. Extrapyramidal signs, behavioural change
C9ORF72	Behavioural change, psychiatric symptoms
GRN	Language led, can cause asymmetric atrophy and white matter change
PRNP - **particularly octapeptide repeat expansions**	Ataxia, myoclonus Peripheral and autonomic neuropathy and chronic diarrhoea with some mutations
CADASIL *(NOTCH3)*	White matter change (anterior temporal, external capsule), migraine, strokes
CSF1R	Behavioural change, pyramidal dysfunction, white matter change, cerebral calcification
Familial British and Danish dementias: FBD and FDD (*ITM2B/BRI2*)	Ataxia, pyramidal dysfunction, white matter change, amyloid angiopathy Stroke-like episodes and rarely intracerebral haemorrhage in FBD Cataracts and deafness in FDD
Hereditary Spastic Paraplegia (particularly type 3)	Pyramidal dysfunction, ataxia
Spinocerebellar Ataxia (particularly 2,12,17)	Ataxia, extrapyramidal signs
Other FTD genes: *VCP, SQSTM1, TARDBP*	Behavioural change, motor neurone disease, Paget's disesase

Mutations where phenotype can be especially similar to familial Alzheimer's disease highlighted in bold. CADASIL = Cerebral Autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Table 2:
FTD genes and phenotype

FTD gene	Typical clinical presentation	Supportive Features
C9ORF72	bvFTD +/- MND, or MND alone. Less commonly nfvPPA, or parkinsonian disorder.	Psychiatric features such as anxiety, apathy, delusions and hallucinations, and/or family history of psychiatric disorders (as can mimic bipolar disorder or schizophrenia). Motor symptoms common, usually attributable to comorbid MND, or more rarely parkinsonism. Very rarely can be a hyperkinetic movement disorder ('HD phenocopy'). Early executive dysfunction and can be slowly progressive. Memory impairment can be a prominent and early feature. Can have parietal dysfunction. **MRI**: Fronto-temporal and sometimes more posterior volume loss. Can also have thalamic and cerebellar atrophy
GRN	bvFTD or PPA syndrome, either nfvPPA or a mixed phenotype. Less commonly FTD-CBS.	Psychiatric features may occur in some. Motor impairment, if present, usually attributable to parkinsonism. Parietal dysfunction common. **MRI**: Fronto-parietal atrophy; very commonly asymmetric. White matter hyperintensities in some cases.
MAPT	bvFTD, which may evolve into an FTD overlap syndrome either FTD-CBS, or more rarely FTD-PSP.	Motor impairment, if present, usually attributable to parkinsonism. Early episodic memory and naming impairment in some cases. **MRI**: symmetric anterior and medial temporal lobe atrophy in many; can be more frontal and lateral temporal lobe atrophy in others
TBK1	FTD-MND or MND alone. Less commonly PPA (nfv and sv) or FTD-CBS.	Psychiatric features may occur. MND features common. Parkinsonism sometimes seen. MRI: can be focal asymmetric temporal lobe atrophy
VCP	Inclusion Body myopathy, Paget's disease, FTD (usually bvFTD phenotype)	Can rarely develop MND and parkinsonism
CHMP2B	bvFTD	Dynamic aphasia has been reported. Parkinsonism, dystonia and myoclonus can occur.
TARDBP	FTD-MND or MND alone. FTD phenotype: bvFTD or svPPA	MND features. Can develop parkinsonism. **MRI**: focal temporal lobe atrophy.
SQSTM1	bvFTD-MND or MND alone.	Paget' disease
FUS	MND alone or FTD-MND.	*FUS* mutations cause familial MND, with concomitant dementia in a minority. However early onset FTD due to FTLD-FUS is typically a sporadic condition. Young age at onset: 40–50s.

MND: motor neurone disease; bv: behavioural variant; nfv: non-fluent variant; PPA: primary progressive aphasia; FTD: frontotemporal dementia; CBS: corticobasal syndrome; sv: semantic variant; HD: Huntington's disease; PSP: progressive supranuclear palsy

Table 3: Monogenic forms of cerebral small vessel disease and additional (non-vascular) inherited white matter disorders that can present with cognitive impairment

Disease	Gene	Inheritance Pattern	Age at onset	Additional neurological features	Extra-neurological manifestations
Monogenic forms of cerebral small vessel disease					
CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)	*NOTCH 3*	AD	20s-70s	Migraine with aura, gait disturbance, seizures.	Psychiatric disorders
CARASIL (cerebral autosomal recessive arteriopathy with sub-cortical infarcts and leukoencephalopathy) and CADASIL2 (AD)	*HTRA1*	AR/AD	AR: 10s -40s; AD: 30s to 60s	Seizures, Parkinsonism, UMN signs	Psychiatric disorders, alopecia, spondylosis
CARASAL (Cathepsin A–related arteriopathy with strokes and leukoencephalopathy)	*CTSA*	AD	30s-60s	Ischaemic and haemorrhagic strokes, migraine, brainstem syndrome	Therapy-resistant hypertension
Retinal Vasculopathy with cerebral leukodystrophy	*TREX1*	AD	40s-50s	Migraine with aura, seizures, UMN signs	Renal and hepatic dysfunction, retinopathy, psychiatric manifestations, Raynaud's, osteonecrosis
COL4A -related arteriopathy	*COL4A1*, *COL4A2*	AD	Infancy to late adulthood	Intracranial haemorrhage, porencephaly, seizures, migraine with aura, UMN signs	Retinopathy, cataracts, psychiatric disturbance, renal impairment
Fabry disease	*GLA*	X-linked recessive	30s–50s(M)/	Stroke, neuropathy	Cardiac involvement,

			40s–50s (F)		renal impairment, psychiatric disturbance, skin changes.
Additional (non-vascular) inherited white matter disorders					
CSF1R-related leukoencephalopathy	*CSF1R*	AD	20s-80s	Gait disturbance, parkinsonism, ataxia, UMN signs	Psychiatric disorders
Alexander disease	*GFAP*	AD	Childhood to late adulthood	Prominent brainstem atrophy (tadpole sign)	
Vanishing white matter disease	*EIF2B1-5*	AR	Childhood to late adulthood	Episodes of severe neurological deterioration after trivial insult	
Adult polyglucosan body disease	*GBE*	AR	>40s	Prominent posterior fossa, brainstem signal change, neuropathy	Bladder and autonomic involvement

Further reading

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Figure legends

Figure 1
Algorithm for genetic testing in frontotemporal dementia (FTD). Consider offering genetic testing to all individuals with behavioural variant FTD (bvFTD) or FTD-motor neurone disease (FTD–MND), even in the absence of a family history. Consider offering genetic testing to individuals with FTD-primary progessive aphasia (FTD-PPA) who have either a strong family history or an atypical phenotype. Consider offering genetic testing to individuals with FTD-progressive supranuclear palsy (FTD-PSP) and FTD-corticobasal syndrome (FTD-CBS)who have a strong family history.

Figure 2 outlining key components of pre-test counselling discussions.

Figure 3 outlining considerations when communicating genetic test results