Review

Genetics of dementia

Clement T Loy, Peter R Schofield, Anne M Turner, John B J Kwok

School of Public Health, University of Sydney, Sydney, NSW, Australia (C T Loy FRACP); Neuroscience Research Australia, Randwick, NSW, Australia (C T Loy, Prof P R Schofield DSc, J B J Kwok PhD); Huntington Disease Service, Westmead Hospital, Westmead, NSW, Australia (C T Loy); University of New South Wales, Kensington, NSW, Australia (Prof P R Schofield, J B J Kwok); and Department of Medical Genetics, Sydney Children's Hospital, Randwick, NSW, Australia (A M Turner FRACP)

Correspondence to:
Dr John B J Kwok, Neuroscience Research Australia, Barker Street, Randwick, NSW 2031, Australia
j.kwok@neura.edu.au

25% of all people aged 55 years and older have a family history of dementia. For most, the family history is due to genetically complex disease, where many genetic variations of small effect interact to increase risk of dementia. The lifetime risk of dementia for these families is about 20%, compared with 10% in the general population. A small proportion of families have an autosomal dominant family history of early-onset dementia, which is often due to mendelian disease, caused by a mutation in one of the dementia genes. Each family member has a 50% chance of inheriting the mutation, which confers a lifetime dementia risk of over 95%. In this Review, we focus on the evidence for, and the approach to, genetic testing in Alzheimer's disease (*APP*, *PSEN1*, and *PSEN2* genes), frontotemporal dementia (*MAPT*, *GRN*, *C9ORF72*, and other genes), and other familial dementias. We conclude by discussing the practical aspects of genetic counselling.

Introduction

25% of the general population aged 55 years and older have a family history of dementia involving a first-degree relative.[1] As a consequence of family medical history awareness campaigns and increased media coverage of the mendelian forms of dementia, a frequently asked question in the clinic is "My mother had dementia, do I have 'the gene' and can I test for it?"

Having a family history of dementia does not necessarily mean there is a mendelian form of dementia (or genetic mutation) in the family. In fact, mendelian forms of dementia are rare. For instance, there have been just over 500 families with mendelian forms of Alzheimer's disease reported.[2] Thus, most people with a family history of dementia do not need molecular genetic testing and can be reassured.

This Review aims to help clinicians identify the small number of high-risk mendelian families and reassure the low-risk majority. It also aims to help clinicians make informed choices when prioritising genetic testing for the mendelian families.

Mendelian diseases versus complex diseases

Families share environmental and genetic influences, so familial diseases might not always be genetic in origin. The most striking example of an environmental factor causing familial dementia is kuru. Kuru is an infectious prion disease that was found in the 1950s in the Papua New Guinea highlands, where relatives consumed the deceased in funeral rituals. This illness was initially thought to be genetic because of familial segregation[3] until experimental work showed that it is a transmissible spongiform encephalopathy. However, overall, the known risk factors for familial dementia are overwhelmingly genetic.

Genetic factors can contribute to familial dementia in two ways: by causing mendelian forms of dementia or as a contributing factor towards genetically complex disease.

Mendelian diseases

A mendelian, or single-gene, disease is due to a mistake or mutation in one of the 25 000 genes in the nuclear genome (figure 1). Many such genes were discovered in family genetic studies called linkage studies. In a linkage study, the location of a disease-causing gene is found by matching the inheritance pattern of disease in a family and the inheritance pattern of genetic location markers. The results of these studies are reported in logarithm of the odds scores, where a score of over 3 is regarded as significant evidence for linkage.[4]

Mendelian diseases: clinical implications

Since the known genes that cause mendelian forms of dementia are autosomal dominant with high penetrance, family trees for affected families usually show many affected members in consecutive generations. Genetic testing can be helpful in this context. Although genetic escapees (ie, people who carry a mutation but who do not have dementia at an old age) do exist, in general, people carrying pathogenic mutations have a 95% or greater lifetime risk of dementia. The exact risk varies depending on the associated age of onset within the family and on penetrance of the gene. Penetrance of a gene is defined as the probability that an individual who has inherited a mutation in a disease gene goes on to develop the disease phenotype. People not carrying the mutations would have the same risk of dementia as the general population.

Complex diseases

A genetically complex (also known as polygenic or multifactorial) disease is caused by genetic and environmental factors, individually and in interaction with each other

(figure 1). These genetic factors are genetic variations present in the normal population, and each factor tends to increase disease risk by a small amount only. Well known examples of complex disease include common diseases such as stroke and diabetes: diseases where family history has been traditionally regarded as a risk factor. These genetic variations are usually discovered in genetic association studies, which comprise association studies for candidate genes and genome-wide association studies (GWAS). In a genetic association study, the frequency of a genetic variation among people with disease is compared with that in a normal control group. In association studies examining candidate genes, the genotyped variations usually have a known biological function relevant to disease pathogenesis. By contrast, genetic variations in GWAS are chosen for their locations throughout the genome—thus, they might have regulatory rather than direct roles in gene functioning or might even have no functional significance at all. The results of these studies are reported as odds ratios (ORs). Typically, the OR for a genetic variation is less than 2, suggesting a small effect. Further background on molecular genetics and GWAS can be found on the Human Genome Project website[5] and in other reviews.[6]

Complex diseases: clinical implications

Since many genetic variations of small effect and environmental factors are needed to cause complex disease, the pattern of inheritance in complex disease is not straightforward. In mendelian diseases, passing on of the one genetic fault to the offspring is sufficient to cause disease, and parent–child transmission can be seen in the family tree. A person with a genetically complex disease is unlikely to pass on every one of the many genetic variations to her or his offspring. However, because these genetic variations are common, the offspring might also inherit other risk-conferring genetic variations from the other parent. Consequently, genetically complex diseases can skip a generation, and there can be people affected on both sides of the family. Genetic testing for any individual genetic variation has poor predictive power for dementia and is not recommended in clinical practice. There has been some interest in testing panels of genetic variations for individual diseases, but the known genetic variations only account for a small proportion of the overall genetic risk, and doing this would be premature in view of the present state of scientific knowledge.[7]

A framework for genetic testing in dementia

The first step in considering molecular genetic testing for dementia is to obtain a detailed and accurate family history, to identify families with family histories consistent with mendelian rather than complex inheritance. These are the families who will benefit most from genetic testing. The second step is to obtain an accurate phenotype for the family to inform the choice of genetic
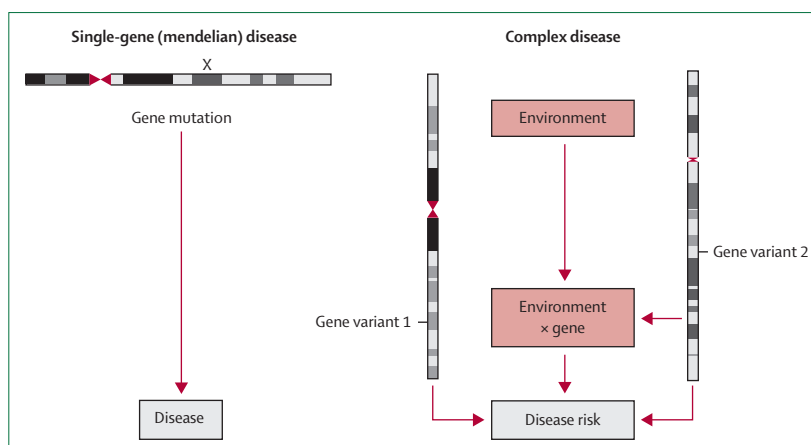

Figure 1: **Pathogenesis in mendelian versus complex disease**
In a mendelian disease, mutation in one gene is necessary and sufficient to cause disease. In a complex disease, normal variations in several genes interact with the environment to increase disease risk.

test. Genetic testing can then be considered, ideally starting with an affected family member.

Obtaining an accurate family history

Obtaining a detailed and accurate family history often involves interviewing many family members. Reporting is more accurate from first-degree than from second-degree or third-degree relatives;[8] thus, different informants might be needed for different branches of the family. Surviving spouses of older affected family members are often important sources of information for the earlier generations, including countries of origin, which might help inform choice of genetic test. Maiden names of affected family members can prove crucial in connecting with other mendelian families with a common founder. Establishing where family members lived is also important. Age and mode of death should be noted for all family members because early death can mask the transmission of mutations through the family tree. Obtaining written medical records for key family members can be helpful because informants are less accurate in reporting the presence of disease in relatives than the absence of disease in relatives.[8] Features in the family history that can help distinguish mendelian from complex disease are discussed in disease-specific sections in this Review.

Obtaining an accurate phenotype

A detailed history of dementia phenotype is also important, and there are validated retrospective informant-based questionnaires that might be helpful.[9,10] Psychiatric history is an integral part of the family history of disease, especially for frontotemporal dementia.[11] An accurate record of age of onset is particularly helpful for families with a history of Alzheimer's disease. Precise classification of dementia phenotype and associated neurological features is helpful for families with a history of frontotemporal dementia. Estimation of age of onset can

be achieved by a semi-structured interview in which family members are asked about the age of first progressive cognitive decline.[12] Travelling to assess living affected family members in person can be informative. For a comprehensive guide to clinical assessment of young-onset dementia, see Rossor and colleagues.[13] Genetests[14] also provides a useful online database of disease-specific guides on genetic testing and a directory of relevant laboratories undertaking the tests. Finally, histopathological diagnosis in a family member can be invaluable. Some Alzheimer's disease mutations can have atypical presentations, suggesting a non-Alzheimer's disease clinical diagnosis,[15] and histopathological diagnosis can also help identify the subtype of frontotemporal dementia in a family.

Considerations for genetic testing

The first person to be tested in a family must be an affected individual. If a pathogenic mutation is detected, this will confirm the diagnosis at the molecular level and makes testing available for other family members. Although requests are often made to test unaffected individuals, a normal or negative genetic test result in a clinically unaffected family member cannot confirm her or his status as a non-mutation carrier unless the causative mutation in the family is known. Patient knowledge of genetics and inheritance can be variable. To hear an individual in a mendelian family say that she or he has a "100% chance" of developing dementia, when the true risk of carrying the mutation is only 50%, is not uncommon.[16] Thus, early consultation with a geneticist can be helpful. Further discussion on genetic counselling can be found later in this Review. In the event of a negative result for a genetic test in patients with a strong family history of disease, a possible strategy would be to suggest that they participate in genetic research that might ultimately result in the discovery of the causative gene.

Genetic testing for Alzheimer's disease

Clinically, typical Alzheimer's disease is characterised by gradual onset and progressive impairment of episodic memory and at least one other cognitive domain (the 1984 National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] criteria).[17] These diagnostic criteria have been revised to recognise non-amnestic presentations of Alzheimer's disease (with language, visuospatial, or executive dysfunction) and the supportive role of biomarkers (the 2011 National Institute on Aging–Alzheimer's Association [NIA-AA] criteria).[18]

Identification of families with mendelian forms of Alzheimer's disease

Mendelian forms of Alzheimer's disease are rare: there are over 35 million people living with Alzheimer's disease in the world,[19] but genetic mutations have been reported so far in only just over 500 families with a history of Alzheimer's disease.[2] For Alzheimer's disease, the key elements in the family history that will help separate mendelian from genetically complex forms of the disease are multigenerational inheritance and a young age of onset (table 1).[20] Families with multigenerational young-onset Alzheimer's disease are the most likely ones to carry a pathogenic mutation in one of the recognised Alzheimer's disease genes. For instance, Raux and colleagues[21] sequenced a cohort of 65 families with a history of early-onset Alzheimer's disease (<60 years) with affected family members in three generations. 86% of these families had mutations in genes that cause Alzheimer's disease: 78% with sequence mutations and 8% with pathological duplication of one of the genes that cause Alzheimer's disease.[22] However, families satisfying this criterion are rare: the prevalence is about 5 per 100 000 people for the 41–60-year-old age group.[23]

If the multigenerational inheritance criterion is relaxed, the yield for mutations will be lower. Janssen and colleagues[24] sequenced a cohort of 31 families that included a family member with early-onset Alzheimer's disease (<61 years), but he or she was only required to have one or more affected first-degree relative. 68% of these families had mutations in genes that cause Alzheimer's disease. If the cohort was restricted to the 23 families with a history of early-onset Alzheimer's disease with three or more family members in at least two generations, then the yield for mutation testing would have been 78%.

If the age of onset criterion is relaxed, the yield for mutations will be lower still. Zekanowski and colleagues[25] sequenced a cohort of 39 individuals, each with early-onset Alzheimer's disease (defined as <65 years rather than <60 years) and one or more first-degree relatives with early-onset Alzheimer's disease. Only 15% of these individuals carried pathogenic mutations. Lleo and colleagues[26] included 30 families with late-onset Alzheimer's disease (>65 years) in their mutation screen. Each of these families had at least two first-degree relatives with Alzheimer's disease, but none had three family members affected in two generations. None of these families had mutations.

In rare instances, mutations[27] or rare variants[28] can be identified in patients from families with a mean age of

	Age of onset	Probability of having a genetic mutation
Affected family members in three generations	<60 years	86%
Two or more affected first-degree relatives	<61 years	68%
Two or more affected first-degree relatives	<65 years	15%
Two or more affected first-degree relatives	>65 years	<1%

Table 1: Probability of finding a pathogenic mutation in one of the recognised Alzheimer's disease genes among multiplex families

onset of Alzheimer's disease later than 65 years. However, these families will contain an increased number of mutation-free individuals with sporadic forms of the disease, who might need a more detailed explanation during genetic counselling.

Finally, among people with early-onset Alzheimer's disease but no family history, mutations in the known Alzheimer's disease genes are rare. Nonetheless, there are documented examples of mutations in this patient group, and some are thought to have arisen de novo.[29] Additionally, non-paternity and reduced penetrance can also conceal a family history of Alzheimer's disease. Although routine testing of people with early-onset Alzheimer's disease with no family history would not be fruitful, a genetic cause should remain in the differential diagnosis, particularly for people with an age of onset of 40 years or younger.

Genetic testing for families with mendelian forms of Alzheimer's disease

Apart from multigenerational inheritance and young age of onset, mendelian forms of Alzheimer's disease tend to present with a similar clinical picture to the other forms of Alzheimer's disease, although myoclonus in the early stages of disease can be a diagnostic clue.[30]

There are three known causative genes for Alzheimer's disease: *APP*, *PSEN1*, and *PSEN2*. Based on the finding that people with trisomy 21 (Down's syndrome) develop dementia with similar histopathological abnormalities to Alzheimer's disease, and supported by genetic linkage, *APP* on chromosome 21 was first proposed to be a candidate gene for Alzheimer's disease in 1987.[31] However, families with *APP* mutations were not identified until 1991.[32] The histopathological hallmarks of Alzheimer's disease (including the mendelian forms of Alzheimer's disease) are plaques and tangles. *APP* breaks down to form amyloid-β, the key component of plaques. This finding led to the amyloid hypothesis, which proposes that amyloid-β production and degradation is not only the cause of this particular mendelian form of Alzheimer's disease, but also of Alzheimer's disease in general. Subsequently, family linkage studies identified two additional genes that cause Alzheimer's disease: *PSEN1*[33] on chromosome 14 and *PSEN2*[34,35] on chromosome 1. Both of these genes either increase amyloid-β production or, in some mutations, alter the ratio of the amyloid-β_{1-42} aminoacid isoform to amyloid-β_{1-40} aminoacid isoform concentrations.[36] These findings form the basis of the amyloid hypothesis (figure 2), which is further supported by the opposite situation, in which an *APP* mutation, which reduces amyloid formation, is protective against Alzheimer's disease.[37] The amyloid hypothesis remains the dominant paradigm in Alzheimer's disease research, although the pathogenesis of Alzheimer's disease in general is probably more complex.[38,39]

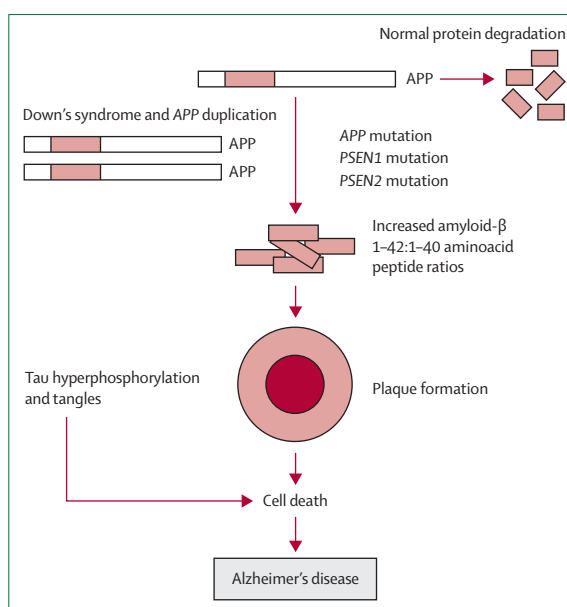86% of families with young-onset (<60 years) dementia in three or more generations have a mutation in the *APP*,

Figure 2: **The amyloid hypothesis and pathogenesis in Alzheimer's disease**
All three of the genes that cause Alzheimer's disease are involved in amyloid-β production, although other factors probably also play a part in the pathogenesis of Alzheimer's disease in general. The amyloid peptide (coloured bar) is cleaved from its precursor protein (open bar) and deposited as senile plaques (coloured circles). APP=amyloid precursor protein.

PSEN1, or *PSEN2* gene.[21,22] Mutation in *PSEN1* is the most frequent cause, accounting for about 60% of mendelian families.[21,24] About 15% of mendelian families have sequence mutations in *APP*,[21,24] although duplication of the *APP* gene might account for another 8% of these families.[22] Mutations in *PSEN2* are rare, with only 22 families reported so far.[2] Our practice is therefore to screen for *PSEN1* mutations first, particularly if the patients have early age of onset, followed by *APP* mutations. Additionally, there are a few phenotypic clues that can help prioritise mutation screening. Families with Alzheimer's disease and spastic paraparesis are likely to have a *PSEN1* mutation and variant histopathological abnormalities characterised by so-called cotton wool plaques.[40] *APP* mutations can also cause cerebral amyloid angiopathy with cerebral haemorrhage.[41] A large proportion of families with *PSEN2* are of Volga German origin. Unlike for *PSEN1* and *APP*, age of onset for *PSEN2* families can be as late as the 70s, and there are also examples of mutation carriers being dementia free in their 80s.[42] If sequencing of all three genes is normal for a mendelian family, then mutation of the *APP* gene by duplication should also be considered.[22]

Finally, care should be taken when a genetic change is found in a new family, because some of these changes might only be polymorphisms with no clinical significance. The genetic change should be checked against the Alzheimer's disease and frontotemporal dementia mutation database,[2] which provides an up-to-date and exhaustive repository of reported
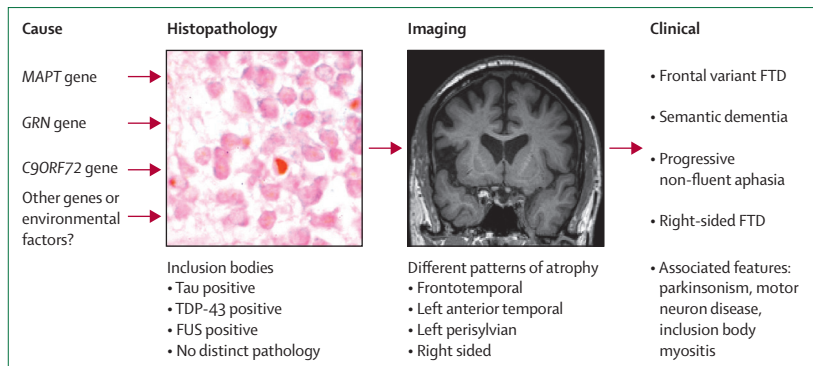
Figure 3: **Frontotemporal dementia**
FTD is a group of disorders characterised by degeneration of the frontal or temporal lobes, or both, but is heterogeneous in clinical presentation, imaging features, underlying histopathological subtypes, and genetics among the mendelian families. FTD=frontotemporal dementia. TDP-43=transactive response DNA binding protein-43. FUS=fused in sarcoma protein.

mutations for each gene. For genetic changes that have not been reported in the past, Guerreiro and colleagues[43] proposed a systematic algorithm to identify the probable pathogenicity of genetic variants, on the basis of segregation within the family, its frequency in clinically normal individuals, and functional studies in model systems.

Advice for families without a mendelian family history of Alzheimer's disease

Although most people with Alzheimer's disease do not have mutations in these known genes, there are many other genetic variations that contribute to disease risk, in a genetically complex manner.

Among these, *ApoE* has the greatest effect, and the evidence for this association is the best replicated. Compared with people with the common *ApoE* E3/E3 genotype, people with the *ApoE* E2/E2, E3/E4, and E4/E4 genotypes are 0·5, three, and eight times more likely to develop Alzheimer's disease, respectively.[44] Nonetheless, up to 75% of people carrying one copy of the high-risk E4 allele remain free of Alzheimer's disease, and up to 50% of people with Alzheimer's disease do not carry the high-risk E4 allele.[45] Thus, testing of the *ApoE* genotype is not recommended. Candidate gene studies and, more recently, GWAS, have identified several additional genetic variations associated with Alzheimer's disease. However, only a small proportion of these variations have been confirmed in replication studies, and the replicated variations have even smaller effects on disease risk than does *ApoE* (OR <2).[46,47]

Recently, a rare variant in the *TREM2* gene was also shown to have a significant association with Alzheimer's disease, with an OR of around 3.[48,49] Mutations in the *TREM2* gene are typically associated with the rare bone and brain disease Nasu-Hakola disease; however, they can also lead to early-onset dementia without bone lesions.[50] Similar to *ApoE*, the *TREM2* rare variant is unlikely to be used for clinical testing.

How then should we advise people with a non-mendelian family history of Alzheimer's disease? Green and colleagues[51] undertook a clinic-based study that included 2594 probands with Alzheimer's disease. They compared the cumulative dementia risk in the probands' first-degree relatives against the probands' spouses as controls. People with a first-degree relative with Alzheimer's disease had roughly 2·5 times the lifetime risk of dementia compared with the general population. For the white subgroup, in absolute terms, the cumulative risk of dementia (by the age of 80 years) was about 18% and 6% for first-degree relatives and spouses of probands, respectively. For the African-American subgroup, the risks were 30% and 13%, respectively.

Genetic testing for frontotemporal dementia

Frontotemporal dementia is a heterogeneous group of disorders, characterised by progressive degeneration of the frontal or temporal lobes, or both. Clinically, it is characterised by progressive deterioration in behaviour, speech production, or language, with relative sparing of memory and visuospatial function.[52,53] Frontotemporal dementia is heterogeneous in clinical presentation, imaging features, underlying histopathological sub-types, and genetics among the mendelian families (figure 3). Although there are general rules linking clinical presentations to imaging findings,[54,55] pathological subtypes[56] and genetic causes,[57] these rules tend to have exceptions and there is not necessarily a one-to-one correspondence. Additionally, there is also some overlap between frontotemporal dementia and two groups of neurodegenerative disorders—motor neuron disease and two of the Parkinson-plus syndromes (corticobasal syndrome and progressive supranuclear palsy). A comprehensive family history, expert pheno-typic classification, and ideally histopathological diag-nosis in a family member will all help prioritise which gene or genes to test. Imaging can be helpful in genetic studies for frontotemporal dementia because it helps refine the patient phenotype and also offers a way of assessing family members who cannot be assessed in person. Additionally, imaging from deceased family members can help relevant diagnoses to be made retrospectively. For more information about frontotemporal dementia, see panel 1.

Identification of mendelian families in frontotemporal dementia

In broad terms, 40–50% of people with frontotemporal dementia have family histories of dementia and related disorders, which might include other neurological or psychiatric diseases.[65] However, the proportion of people with an autosomal dominant family history is lower (10–30%).[65] As with Alzheimer's disease, families with multigenerational inheritance and young onset are more likely have genetic mutations. This is well illustrated by the Queen Square series (Dementia Research Centre, London,

Panel 1: Frontotemporal dementia

Clinically, frontotemporal dementia is a heterogeneous group of syndromes characterised by progressive deterioration in behaviour, speech production, or language, with relative sparing of memory and visuospatial function.[52,53] Frontotemporal dementia can be subdivided into three clinical subtypes: behavioural-variant frontotemporal dementia, progressive non-fluent aphasia, and semantic dementia. Progressive non-fluent aphasia and semantic dementia are sometimes grouped together under the umbrella term primary progressive aphasia. The Neary criteria[52] remain a helpful description of the clinical subtypes of frontotemporal dementia. However, there are revised criteria for behavioural-variant frontotemporal dementia, which are likely to improve the sensitivity and specificity of clinical diagnosis.[58] These criteria incorporate imaging and genetic data, thus allowing earlier diagnosis in some cases and exclusion of other non-progressive cases. Another development is the recognition of a third subtype of primary progressive aphasia, the logopenic variant,[59] which is characterised by slow and reduced verbal output with sparing of grammar, and word finding difficulties without impairment in single word comprehension. As such, this group of patients seems to be distinct from progressive non-fluent aphasia and semantic dementia, although only a small proportion of patients with non-progressive non-fluent aphasia and non-semantic dementia fit into this subtype.[60] Generally speaking, these clinical subtypes are associated with specific imaging findings (figure 3).[54]

Clinical subtypes are also associated with specific histopathological subtypes to a certain amount, although clinical prediction of underlying histopathological changes is not straightforward. The nomenclature of histopathological subtypes of frontotemporal lobar degeneration (FTLD) was updated in 2010.[61] FTLD histopathological subtypes are classified according to immunohistochemical reactivity to many proteins, including tau (FTLD-tau), transactive response DNA binding protein-43 (FTLD-TDP), and fused in sarcoma protein (FTLD-FUS). Before discovery of the roles of TDP and FUS in FTLD, FTLD-TDP and FTLD-FUS were both classified as FTLD with ubiquitinated inclusions (FTLD-U). The small number of FTLD-U cases that do not stain positive for TDP or FUS are now denoted FTLD-ubiquitin proteasome system (FTLD-UPS). Semantic dementia has the most consistent underlying histopathological changes: 75% of cases in a histopathological series had FTLD-U, and the retrievable cases were all TDP positive.[62] Histopathological findings are much more variable for behavioural-variant frontotemporal dementia (can be any of the FTLD subtypes) and progressive non-fluent aphasia (FTLD-tau or FTLD-TDP). Also, these clinical subtypes are not 100% specific for FTLD, and other neurodegenerative diseases such as Alzheimer's disease can also mimic frontotemporal dementia, progressive non-fluent aphasia, and semantic dementia clinically. Other clues for clinicohistopathological associations include the finding that frontotemporal dementia associated with motor neuron disease is associated with FTLD-TDP[63] and that frontotemporal dementia with very early age of onset without a family history may predict FTLD-FUS.[64]

The relation between genetic mutations and histopathological abnormalities is more predictable than the relation between clinical subtype and histological changes. In general, mutations in a specific gene only lead to one histopathological subtype (table 2). Histopathological diagnosis in a family member is invaluable in genetic studies, because it will provide greater certainty than prediction of histological abnormalities by clinical subtype alone.

UK), in which a cohort of 256 probands with frontotemporal dementia were classified according to pattern of family history and were screened for pathogenic mutations in the genes that cause frontotemporal dementia.[66,67] 88% of patients with the strongest autosomal dominant family history carried such mutations. These families were characterised as having at least three affected family members in two generations specifically with frontotemporal dementia, motor neuron disease, or one of the Parkinson's plus syndromes (corticobasal syndrome or progressive supranuclear palsy). Additionally, one affected person must also be a first-degree relative of the other two affected family members. For the patient group in which three or more family members had dementia in general, but not satisfying the aforementioned criteria, 41% had mutations. The probability of finding a mutation for patients with only one family member with dementia depended on the age of onset of the relative. 31% of patients with one relative with dementia before the age of 65 years had mutations. By contrast, only 13% of patients

with one relative with dementia after the age of 65 years had mutations. Only 7% of patients with no contributory family history had mutations.

Genetic testing for families with mendelian forms of frontotemporal dementia

Three causative genes explain over 80% of cases of frontotemporal dementia in families with a strong autosomal dominant family history:[66] *MAPT*, *GRN*, and *C9ORF72*. *MAPT* was the first to be discovered in 1998.[68] It was discovered using a positional cloning approach among families linked to chromosome 17 who presented with frontotemporal dementia and parkinsonism. Tau is a microtubule binding protein involved in the transport of organelles and other cellular components. Mutations in *MAPT* can either disrupt tau protein structure or alter the proportion of different tau isoforms available. These events lead to impaired microtubule assembly, impaired axonal transport, and can promote pathological tau filament aggregation.[69] The fact that many other

families with chromosome-17-linked frontotemporal dementia did not have *MAPT* mutations, and had ubiquitin rather than tau-based histopathological abnormalities, was soon realised. In 2006, these families were shown to have mutations in the *GRN* gene.[70,71] Most mutations in *GRN* are null mutations that lead to nonsense-mediated decay of mutant *GRN* mRNA and reduced expression of progranulin. Consequently, mutation carriers can be identified by measuring serum progranulin concentrations.[72] Progranulin is a glycoprotein with a range of cellular regulatory functions; its exact role in neurodegeneration is still being investigated.[73] Finally, in 2011, several chromosome-9-linked families with frontotemporal dementia, motor neuron disease, or both, had expanded GGGGCC hexanucleotide repeats in the intronic region of the *C9ORF72* gene.[74,75] Affected members from these families had transactive response DNA binding protein-43 (TDP-43)-based pathological abnormalities. Fewer than 20 repeats is regarded as normal;[75] however, there are now examples of people with normal cognition and more than 30 repeats.[76] Although the typical pathogenic *C9ORF72* repeat is in the hundreds, the lower limit of the pathogenic range might be as low as 65 repeats.[76] There are families with both mutations in *C9ORF72* and other genes related to motor neuron disease, which suggests that motor neuron disease might be oligogenic in nature.[77] The pathogenesis of *C9ORF72*-related frontotemporal dementia is still being elucidated. The function of the C9ORF72-encoded protein is unknown, but the GGCCCC repeats do form nuclear RNA foci in affected cells.[74] This finding suggests a shared RNA-mediated neurodegenerative mechanism with other non-coding repeat expansion disorders.

MAPT, *GRN*, and *C9ORF72* all cause disease in an autosomal dominant manner. Mutations in *C9ORF72* tend to be the most common, with a lower but similar proportion of people carrying *GRN* and *MAPT* mutations in most case series.[57] For instance, the Mayo Clinic familial frontotemporal dementia series identified 11·7%, 7·6%, and 6·3% of people carrying *C9ORF72*, *GRN,* and *MAPT* mutations, respectively.[74] *GRN*[78] and *C9ORF72*[79] can be associated with reduced penetrance and are both found in apparently sporadic cases. Moreover, *C9ORF72* seems to be more common in patients with familial motor neuron disease of European ancestry (39%) and rarer in comparable east Asian patients (5%).[80]

In addition to the three main frontotemporal dementia-causing genes, there are many rarer genetic causes of frontotemporal dementia. Mutations in the chromosome 9 *VCP* gene cause autosomal dominant frontotemporal dementia together with inclusion body myositis and Paget's disease of the bone.[81] Mutations in the chromosome 16 *FUS* gene most commonly cause motor neuron disease without dementia,[82] although *FUS* mutations have also been associated with clinical frontotemporal dementia.[83] People with frontotemporal dementia and FUS histopathological abnormalities tend not to have mutations in the *FUS* gene.[84] A mutation in the chromosome 3 *CHMP2B* gene has been found in a large autosomal dominant Danish frontotemporal dementia pedigree,[85] but is very rare otherwise. People with *CHMP2B* mutations also have unusual ubiquitin-positive but TDP-negative and FUS-negative pathological abnormalities (frontotemporal lobar degeneration–ubiquitin proteasome system).

Clinical frontotemporal dementia has also been reported in people with mutations in several genes typically associated with other diseases. These include the chromosome 2 dynactin-1 gene,[86] presenilin-1 gene,[87,88] and the chromosome 1 *TARDBP* gene.[89]

Genotype–phenotype correlation for the frontotemporal dementia genes has been summarised in two excellent reviews.[57,90] Although there is strict correspondence between causative gene and histopathological changes, there is much overlap in the relation between causative gene and clinical presentation, and one might not be able to predict the causative gene on the basis of phenotype alone. For instance, all three of the main frontotemporal dementia genes can cause behavioural-variant frontotemporal dementia or have parkinsonism as part of the clinical presentation. Our practice is therefore to use histopathological data when available and then prioritise gene testing according to some of the more specific phenotypes associated with each causative gene (table 2). Although the typical family with a history

	Suggestions for prioritised genetic testing
Histopathology available	FTLD-tau (*MAPT*), FTLD-TDP (*GRN* or *C9ORF72*), FTLD-FUS (consider *FUS* mutations, but often absent), FTLD-UPS (*CHMP3B*)
Motor neuron disease is part of the phenotype	*C9ORF72* then *GRN*
Corticobasal syndrome is part of the phenotype	*GRN* then *MAPT*
Psychosis is part of the phenotype	*C9ORF72* and *GRN*
Highly variable age of onset or reduced penetrance	*GRN* and *C9ORF72*
Cerebellar involvement	*C9ORF72*
Other associations	Inclusion body myositis or Paget's disease of the bone (*VCP*). Danish ancestry (*CHMP2B*)

Genetic testing may proceed to other genes if the suggested genes are normal or negative. FLTD=frontotemporal lobar degeneration. FUS=fused in sarcoma protein. TDP=transactive response DNA binding protein-43. UPS=ubiquitin proteasome system.

Table 2: **Clinical clues that might help prioritise genetic testing in familial frontotemporal dementia**

of frontotemporal dementia and motor neuron disease probably has a *C9ORF72* mutation, occasionally motor neuron disease can also occur in families with *GRN* mutations.[91] Traditionally, corticobasal degeneration has been thought to be a tau-based disease, but a corticobasal-degeneration-like clinical picture is not uncommon in families with *GRN* mutations.[92] Consequently, that pattern of signs and symptoms has been renamed corticobasal syndrome, and we suggest considering both *GRN* and *MAPT* when undertaking genetic testing for families with corticobasal syndrome. Psychotic symptoms can occur in up to 38% of people with *C9ORF72* mutations,[93] but hallucinations can also be part of the presentation for people with *GRN* mutations.[78] A somewhat unique finding in families with frontotemporal dementia with *C9ORF72* mutations is cerebellar involvement clinically,[94] by imaging,[95] and on histopathology.[96] This finding might be yet another pointer to testing for *C9ORF72* mutations. There are emerging neuroimaging features that point to underlying genetic mutations on a group-wise basis,[95]

although there is at present no easy way to apply this to individual patients in the clinic.

Finally, in the absence of pathological data, there can be significant overlap in clinical presentation between Alzheimer's disease and frontotemporal dementia.[97] In such cases where the diagnosis is unclear, patients can be advised to have both Alzheimer's disease and frontotemporal dementia genes tested.

Advice for families without a mendelian family history of frontotemporal dementia

For people with a non-mendelian family history of frontotemporal dementia, the most generalisable information for dementia risk comes from a population-based study in the Netherlands.[98] Using a case-finding approach, Stevens and colleagues[98] identified and verified all cases of frontotemporal dementia in a population of 15 million people. Among the 411 first-degree relatives of people with frontotemporal dementia, the cumulative incidence of dementia before age 80 years was 22%. The cumulative incidence was lower (18%) once the

	Comments
Dementia with myoclonus	
Prion (*PRNP*) gene[99]	Genetic prion disease has three clinical subtypes: familial Creutzfeldt–Jakob disease, Gerstmann-Straussler-Scheinker disease, and fatal familial insomnia, with some genotype-phenotype association.[100] Rarely, mutations in the *PRNP* gene can also produce progressive memory loss similar to Alzheimer's disease.[101,102]
Genes that cause Alzheimer's disease	Myoclonus can also present as an early feature in familial Alzheimer's disease.[103]
Dementia with chorea	
Huntingtin (*HTT*) gene[104]	People with Huntington's disease might not present with chorea as the first symptom. Cognitive impairment can precede chorea by decades,[105] and the Westphal variant is characterised by rigidity rather than chorea.[106]
Genes that cause phenotypes similar to Huntington's disease	These include genes that cause spinocerebellar ataxia type 3, spinocerebellar ataxia type 17, dentatorubropallidoluysian atrophy, neuroacanthocytosis, neuroferritinopathy, and Junctophilin-3 mutations.[107,108]
Dementia with ataxia	
Genes that cause cerebellar ataxia[109,110]	Examples of genetic forms of ataxia with cognitive impairment include spinocerebellar ataxia type 2,[111] spinocerebellar ataxia type 3,[112] spinocerebellar ataxia type 17,[113] dentatorubropallidoluysian atrophy,[114] and neuroacanthocytosis. This list is likely to grow.
Dementia with dystonia	
ATPase-7b (*ATP7B*) gene for Wilson disease[115,116]	Wilson disease is autosomal recessive so there might not be a family history. Nonetheless, it is an important differential because it is potentially treatable.[117]
Niemann–Pick disease type C1 (*NPC1*) and *NPC2* genes	Niemann-Pick disease type C is an autosomal recessive lysosomal lipid storage disease that sometimes presents in young adulthood with a spectrum of clinical findings including cognitive impairment, supranuclear ophthalmoplegia, dystonia, ataxia, and splenomegaly.[118] It is diagnosed by biochemical testing of fibroblast culture or genetic testing and is potentially treatable.[119]
Dementia with white matter changes on imaging	
Genes that cause paediatric white matter diseases[120]	In young adults, this feature raises the possibility of metabolic, mitochondrial, and other inherited disorders. The differential is broad, but testing for serum lactate, serum aminoacid, and urinary organic acids, and consulting with a metabolic physician would be a good starting point.
NOTCH3 gene[121]	CADASIL is an autosomal dominant disorder with migraines, young-onset strokes, dementia, and white-matter changes on MRI.[122] Skin biopsy has been used to diagnose CADASIL in the past, but molecular genetic testing is now the preferred method. Although frequently considered as a differential diagnosis, this is a comparatively rare disorder with a prevalence of about two per 100 000 population.[123]
Dementia with PME	
Specific genes for each disease that causes PME[124,125]	This is a heterogeneous group of disorders, which includes myoclonus epilepsy and ragged red fibres, Unverricht-Lundborg disease, Lafora body disease, neuronal ceroid lipofuscinosis, and type 1 sialidosis. In the past, diagnosis required tissue biopsies, but the causative genes have now been found for many of these disorders.

CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. PME=progressive myoclonic epilepsy.

Table 3: Genetic testing for familial dementia with additional neurological features

mendelian families with *MAPT* mutations were excluded (*MAPT* was the only frontotemporal dementia causative gene known at the time). The cumulative incidence was 11% among 2934 first-degree relatives of matched population-based control individuals. In other words, people with a non-mendelian family history of frontotemporal dementia have roughly twice the lifetime risk of dementia compared with the general population, and this increase in risk is similar to that found in relatives of people with Alzheimer's disease.

Genetic testing for familial dementia with additional neurological features

Cognitive impairment is common in neurogenetic disorders, and familial dementia often presents with additional neurological features. Table 3 summarises some of the common neurogenetic disorders with cognitive features, and Rossor and colleagues[13] also provide a comprehensive review.

Two disorders deserve a special mention: Huntington's disease and dementia with Lewy bodies. Huntington's disease is one of the most common neurogenetic disorders[126] and can present without chorea (table 3). This differential is one of the more frequent causes of very-early-onset dementia (onset age 20s–30s), but can be difficult to recognise in the absence of chorea. Dementia with Lewy bodies typically presents in a sporadic manner.[127] However, there is a small increase in risk of dementia with Lewy bodies among siblings of people with dementia with Lewy bodies compared with siblings of people with Alzheimer's disease,[128] and families with an autosomal dominant pattern of inheritance do exist.[129] Dementia is also common in Parkinson's disease,[130] and

considering Parkinson's disease dementia and dementia with Lewy bodies as diseases in the same Lewy body disorder spectrum can be helpful.[131] For the rare families with Lewy body disorder spectrum, testing for genes that cause Parkinson's disease[132] should be considered, especially α-synuclein. Mutations in the *GBA* gene cause the lysosomal storage disease Gaucher's disease in a recessive manner (ie, mutations in both copies of the gene are needed). However, in one case series, 23% of people with pathologically confirmed dementia with Lewy bodies carried one abnormal copy of the *GBA* gene.[133]

Practical aspects of genetic counselling

Genetic testing can be carried out on a symptomatic or on a predictive basis. Symptomatic testing is for people already diagnosed with dementia, whereas predictive testing is for people who are clinically well. Genetic counselling is helpful in both situations, but formal counselling with a geneticist is essential for people undergoing predictive testing. There are several guidelines for genetic testing in Alzheimer's disease and frontotemporal dementia.[20,134]

Generally speaking, symptomatic genetic testing in dementia does not change clinical management; however, it can help confirm the diagnosis if there had been any uncertainty. It is also a good opportunity to give information to the patient's family members and to offer genetic counselling. Panel 2 contains a checklist of information for patients about the genetics of mendelian forms of dementia.

Unaffected individuals tend to request predictive testing for three reasons: memory symptoms, future life planning, and, more specifically, reproductive planning. A neurological review can be helpful, especially for the subgroup of patients with memory symptoms. Formal counselling from a clinical geneticist or genetic counsellor is essential. People who request predictive testing need additional support and information because there is no curative treatment to offer them if they test positive. Examples of support resources can be found on the websites of the UK Alzheimer's Society[135] and the US Alzheimer's Association.[136] Many individuals at 50% risk, when adequately informed, choose not to proceed with testing.

The principles of predictive testing are well established for Huntington's disease, and the 1994 guideline remains a helpful document.[137] In general, predictive testing is only recommended for adults, and testing should be delayed if there is evidence of substantial psychological or psychiatric problems. The person being tested is encouraged to involve a family member or friend as a support person throughout the testing process. She or he should also be aware of the absence of specific preventative interventions if she or he tests positive, and potential harms including psychological harms and difficult access or exclusion from some insurance policies. There should be a substantial time period between information giving and the final decision to test,

and there should also be follow-up counselling after the test. Suicide is a risk in genetic testing, and the Columbia suicide severity rating scale is a helpful assessment in this context.[138] If genetic testing is considered in the context of reproductive planning, the possibilities of prenatal genetic testing and preimplantation diagnosis[139] should be discussed.

Finally, individuals identified as unaffected mutation carriers might also consider the opportunity to join treatment trials for genetic at-risk groups, such as those announced as part of the Alzheimer's Prevention Initiative and Dominantly Inherited Alzheimer Network initiatives.

Conclusions

Dementia is a common disorder, and a family history of dementia is also common. Fortunately, mendelian forms of dementia are rare. Thus, for relatives of most people with dementia, their lifetime risk of dementia is around 20%, compared with about 10% in the general population. However, in the small proportion of families in which there is a strong autosomal dominant family history of early-onset dementia, mutation in one of the dementia-causing genes can often be found. Each offspring of the affected person will then have a 50:50 chance of inheriting the mutation, and with the mutation, a lifetime dementia risk of over 95%.

In this Review, we highlighted the importance of a detailed family history and provided clinical clues to help clinicians prioritise which gene or genes to test first. At present, the specialty of genomic analysis in human inherited disease is undergoing rapid change. The advent of technical advances such as exome sequencing (reading the sequence of the coding regions of every gene in one test) and whole-genome sequencing (reading the entire sequence, coding and non-coding regions, for the human genome in one test)[140] is already transforming the process of genetic testing. These massively parallel sequencing techniques allow us to sequence a large number of genes simultaneously, at the cost of sequencing two or three genes using previous technology. This approach is particularly attractive for disorders for which there are several causative genes with overlapping phenotypes, such as frontotemporal dementia, and removes the need to prioritise genetic testing in a probabilistic manner. This approach has yielded some unexpected results, such as identification of a mutation in the *NOTCH3* gene in a patient with clinical Alzheimer's disease.[141] There are already examples of successful genetic diagnosis with these techniques.[142,143] Although these techniques still need to be validated before routine clinical use and will generate new clinical and ethical dilemmas[144] (eg, interpretation of rare and novel variants), they will revolutionise the way we think about genetic testing and bring us closer to the ideal of personalised medicine.

Contributors
All authors contributed to the writing and reviewing of this manuscript.

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