The Genetics of Dementia

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ABSTRACT

Twenty-five percent of all people, aged fifty-five and over, have a family history of dementia. For most the family history is due to genetically complex disease- where multiple genetic variations of modest effect, interact to increase dementia risk. The lifetime dementia risk for these families is about 20%, compared to 10% in the general population. A small proportion of families have an autosomal dominant family history of early onset dementia. This is often due to Mendelian disease, caused by mutation in one of the dementia genes. Each family member has a 50% chance of inheriting the mutation, and with it, a lifetime dementia risk of over 95%. This review focuses on the evidence for, and our approach to, genetic testing in Alzheimer 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 counseling.

Introduction

Twenty-five percent of the general population, aged fifty-five and over, have a family history of dementia involving a first degree relative.[1] As a consequence of family medical history awareness campaigns, and increasing 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 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 are just over five hundred families with Mendelian forms of Alzheimer Disease (AD) reported in the literature.[2] Thus the vast majority of people with a family history does not require 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. It will begin with an overview of the genetics of Mendelian versus genetically complex diseases, and proceed to describe a framework for genetic testing in dementia. A guide to genetic testing in various dementia subtypes will then be provided, followed by a note on the practical aspects of genetic counseling.

Mendelian diseases versus complex diseases

Families share environmental as well as genetic influences, so familial diseases may not always be genetic in origin. The most striking example of an environmental factor causing familial dementia is Kuru. This is an infectious prion disease found in the New Guinean Highlands in the 1950s, where relatives consumed the deceased in funeral rituals. Indeed this was initially hypothesized to be a genetic illness due to familial segregation,[3] until

experimental work demonstrated that it is a transmissible spongiform encephalopathy. Overall, however, the known risk factors for familial dementia are overwhelmingly genetic. Genetic factors can contribute to familial dementia in two ways- 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 inheritance pattern of genetic location markers. The results of these studies are reported in LOD (logarithm of the odds) scores, where a LOD score of over 3 is regarded as significant evidence for linkage.[4]

Mendelian diseases: clinical implications

Since the known genes causing Mendelian forms of dementia are autosomal dominant with high penetrance, family trees for affected families usually show multiple affected members in consecutive generations. Genetic testing can be helpful in this context. While genetic escapees (i.e. people who carry a mutation but are not demented at an old age) do exist, in general, people carrying pathogenic mutations have a 95% or greater life-time dementia risk. The exact risk would vary depending 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, or polygenic/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 degree only. Well known examples of complex disease include common diseases such as stroke and diabetes: diseases where we have traditionally regarded family history 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 against 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. On the other hand, genetic variations in GWAS are chosen for their locations throughout the genome- so they may have regulatory rather than direct roles in gene functioning, or may 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 <2, indicating relatively modest effect. Further background on molecular genetics and GWAS can be found on the Human Genome Project website[5] and other reviews.[6]

Complex diseases: clinical implications

Since multiple genetic variations of modest effect and environmental factors are required 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 suffices in causing disease, and parent-child transmission is clearly seen in the family tree. A person with a genetically complex disease is unlikely to pass on every one of the multiple genetic variations to her/his offspring. On the other hand, because these genetic variations are common, the offspring may also inherit other risk-conferring genetic variations from the other parent. Consequently genetically complex diseases may 'skip a generation', or have people affected on both sides of the family. Genetic testing for any individual genetic variation has very 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 this would be premature given our current 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, in order 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 in order to inform the choice of genetic test. Then genetic testing can be considered, ideally starting with an affected family member.

Obtaining an accurate family history

Obtaining a detailed and accurate family history often involves interviewing multiple family members. Not surprisingly, reporting is more accurate from first-degree than second- or third-degree relatives,[8] so, different informants may 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 may 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. It is also important to note where family members lived. Age and mode of death should be noted for all family members, as 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 the disease-specific sections below.

Obtaining an accurate phenotype

A detailed history of dementia phenotype is also important, and there are validated retrospective informant-based questionnaires in the literature which may be helpful.[9, 10] Psychiatric history is an integral part of the family history, especially for Frontotemporal Dementia (FTD).[11] An accurate record of age of onset is particularly helpful for AD families, and precise classification of clinical phenotype/ associated clinical features is helpful for FTD families. 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 very informative. For a comprehensive guide to clinical assessment of young onset dementia, see Rossor et al.[13] Genetests[14] also provides a useful online database of disease-specific guides on genetic testing, and a directory of relevant laboratories performing the tests. Finally, histopathologic diagnosis in a family member can be invaluable. Some AD mutations may have atypical presentations suggesting a non-AD clinical diagnosis,[15] and histopathologic diagnosis can also help determine the subtype of FTD in the 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 a molecular level and makes testing available for other family members. Although requests are often made to test unaffected individuals, it is important to appreciate that a normal/negative genetic test result in a clinically unaffected family member cannot confirm her/his status as a non-mutation carrier, unless the causative mutation in the family is known. Patient knowledge in genetics and inheritance can be very variable. It is not uncommon to hear an individual in a Mendelian

family say that she/he has a '100% chance' of becoming demented, when the true risk of carrying the mutation is only 50%.[16] Thus early consultation with a geneticist can be very helpful, and further discussion on genetic counseling can be found at the end of this review. In the event of a negative result for 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 may ultimately result in the discovery of the causative gene.

Genetic testing for Alzheimer Disease

Clinically, typical AD is characterized by gradual onset and progressive impairment of episodic memory, and at least one other cognitive domain (the 1984 NINCDS–ADRDA criteria).[17] Recently, these diagnostic criteria have been revised to recognize nonamnestic presentations of AD (with language, visuospatial or executive dysfunction), and the supportive role of biomarkers (the 2011 NIA-AA criteria).[18]

Who to test? Identifying families with Mendelian forms of Alzheimer Disease

Mendelian forms of AD are rare- there are over 35 million people living with AD in the world,[19] but only just over 500 AD families with genetic mutations reported in the literature to date.[2] For AD, the key elements in the family history which will help separate Mendelian from the genetically complex form of AD are multigenerational inheritance, and a young age of onset[20] (Table 1). Families with multi-generational young onset AD, are the most likely ones to carry a pathogenic mutation in one of the currently recognized AD genes. For instance, Raux et al. [21] sequenced a cohort of 65 early onset AD families (<60 years), with affected family members in three generations. 86% of these families were found to have mutations in the AD causing genes- 78% with sequence mutations, and another 8% with pathologic duplication of one of the AD causing genes[22]. It is noteworthy, however, that

families satisfying this criterion are rare- the prevalence is about 5/100,000 for the 41-60 year old age group.[23]

If the multigenerational inheritance criterion is relaxed, the yield for mutations will be lower. Janssen et al.[24] sequenced a cohort of 31 families, where there was a family member with early onset AD (<61 years), but he or she was only required to have one or more affected first degree relative. 68% of these families were found to have mutations. If the cohort were restricted to the 23 early onset AD families 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 et al.[25] sequenced a cohort of 39 individuals, each with early onset AD (defined as <65, rather than<60 years), and one or more first degree relatives with early onset AD. Only 15% of these individuals were found to carry pathogenic mutations. Lleo et al.[26] included 30 families with late onset AD (>65 years) in their mutation screen. Each of these families had at least two first degree relatives with AD, but none had three family members affected in two generations. None of these families were found to have mutations.

In rare instances, mutations[27] or rare variants[28] can be identified in patients from families with mean age of onset later than 65 years. Although it should be noted that there will be an increased number of mutation free individuals with sporadic forms of the disease, which may require a more detailed explanation during genetic counseling

Finally, among people with early-onset AD but no family history, mutations in the known AD genes are very rare. Nonetheless there are documented examples of mutations in this patient group, and some are thought to have arisen *de novo*.[29] In addition, non-paternity and reduced penetrance can also conceal a family history. While it would not be fruitful to routinely test people with early-onset AD with no family history, a genetic cause should

remain in the differential diagnosis, particularly for people with an age of onset of 40 years or younger.

What to test? Genetic testing for families with Mendelian forms of Alzheimer Disease

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

There are three currently known causative genes for AD: Amyloid Precursor Protein (*APP*), Presenilin-1 (*PSEN1*), and Presenilin-2 (*PSEN2*). Based on the observation that people with Trisomy 21 (Down Syndrome) develop dementia with similar histopathology to AD, and supported by genetic linkage, *APP* on chromosome 21 was first proposed to be a candidate gene for AD in 1987.[31] However it was not until 1991 that families with *APP* mutations were identified.[32] The histopathologic hallmarks of AD (including the Mendelian forms of AD) are plaques and tangles. *APP* breaks down to form amyloid-β, the key component of plaques. This has led to the 'Amyloid Hypothesis', which hypothesized that amyloid-β production and degradation was not only the cause for this particular Mendelian form of AD, but also AD in general. Subsequently, family linkage studies identified two additional AD-causing genes: *PSEN1* [33] on chromosome 14 and *PSEN2* [34, 35] on chromosome 1. Both of these genes have been found to either increase the production of amyloid-β production, or in certain mutations, to alter the ratio of the amyloid β1-42 amino acid isoform to 1-40 amino acid isoform levels.[36] This forms the basis of the Amyloid Hypothesis (Figure 2), which is further illustrated by the opposite situation where an *APP* mutation, which reduces amyloid formation, was found to be protective against AD.[37] The Amyloid Hypothesis has been the dominant paradigm in AD research since, although the pathogenesis of AD in general is likely to be more complex.[38, 39]

Altogether, these three genes account for 86% of AD families with age of onset under 60 in three or more generations.[21, 22] Mutation in *PSEN1* is the most frequent cause- accounting for about 60% of Mendelian families.[21, 24] About fifteen percent of Mendelian families are due to sequence mutations in *APP*,[21, 24] although duplication of the *APP* gene may account for another 8% of these families.[22] Mutations in *PSEN2* are rare, with only 22 families reported in the literature to date.[2] Our practice is therefore to screen for *PSEN1* mutations first, particularly if the patients have very early age of onset, followed by *APP*. There are a few phenotypic clues that may help prioritize mutation screening however. Families with AD and spastic paraparesis are likely to have a *PSEN1* mutation, and a variant histopathology characterized by 'cotton wool plaques'.[40] *APP* mutations can also cause cerebral amyloid angiopathy with cerebral haemorrhage.[41] A great proportion of families with *PSEN2* are of Volga German origin. Unlike *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] Finally, if sequencing of all three genes are 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 may only be polymorphisms with no clinical significance. The genetic change should be checked against the AD&FTD Mutation Database[2], which provides an up to date and exhaustive repository of reported mutations for each gene. If the genetic change has not been reported in the past, Guerreiro et al. has also proposed a systematic algorithm to determine the probable pathogenicity of genetic variants, based on segregation within family, its frequency in clinically normal individuals, and functional studies in model systems.[43]

Advice for the other families

While the vast majority of people with AD do not have mutations in these currently known genes, there are a number of other genetic variations which contribute to disease risk, in a genetically complex manner.

Among these, Apolipoprotein E (*ApoE)* has the greatest effect and the evidence for this is the best replicated by far. Compared to people with the common *ApoE* E3/E3 genotype, people with the *ApoE* E2/E2, E3/E4 and E4/E4 genotypes are 0·5-, 3- and 8-fold more likely to develop AD respectively.[44] Nonetheless, , up to 75% of people carrying 1 copy of the high risk E4 allele remain free of AD, and up to 50% of people with AD do not carry the high risk E4 allele.[45] Thus testing of *ApoE* genotype is not recommended. Candidate gene studies and, more recently, GWAS, have identified a number of additional genetic variations associated with AD. 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 *ApoE* (OR<2).[46,47]

Recently, a rare variant in the *TREM2* gene was also found have a significant association with AD, with an Odds Ratio of around 3.[48, 49] Mutations in the *TREM2* gene are typically associated with the rare bone and brain disease Nasu-Hakola Disease, however it can also lead to early onset dementia without bone lesions.[50] Like *ApoE*, it is unlikely that the TREM2 rare variant will be used for clinical testing.

How then should we advise people with a non-Mendelian family history of AD? Green et al. carried out a clinic-based study, which included 2594 probands with AD.[51] They compared the cumulative dementia risk in the probands' first degree relatives, against the probands' spouses as controls. Having a first degree relative with AD, means that one has a roughly 2·5 times the lifetime risk of dementia, compared to the general population. For the White American subgroup, in absolute terms, they found the cumulative risk of dementia (by the

age of 80) to be 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 (FTD) is a heterogeneous group of disorders, characterised by progressive degeneration of the frontal and/or temporal lobes. Clinically it is characterized by progressive deterioration in behavior, speech production or language, with relative sparing of memory and visuospatial function.[52, 53] FTD is heterogeneous in clinical presentation, imaging features, underlying histopathologic subtypes, and genetics among the Mendelian families (Figure 3). While there are general rules relating clinical presentations to imaging findings,[54, 55] to pathologic subtypes[56] and to genetic causes,[57] these rules tend to have exceptions and there is not necessarily a one-to-one correspondence. In addition, there is also a degree of overlap between FTD and two groups of neurodegenerative disorders- motor neuron disease (MND), and two of the Parkinson-plus syndromes, corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP). A comprehensive family history, expert phenotypic classification, and ideally histopathologic diagnosis in a family member, will all help prioritize which gene(s) to test. Imaging can be very helpful in genetic studies for FTD because it helps refine patient phenotype, and also offers a way of assessing family members who cannot be assessed in person. In addition, imaging from deceased family members may help make relevant diagnoses retrospectively. For more information about FTD, see Panel 1.

Who to test? Identifying Mendelian families in Frontotemporal Dementia

In broad terms, 40-50% of people with FTD have family histories of dementia and related disorders, which may include other neurologic or psychiatric diseases.[58] However, the proportion of people with an autosomal dominant family history is lower (10-30%).[58] As with AD, families with multi-generational inheritance and young onset are more likely have

genetic mutations. This is well illustrated by the Queen Square series, where a cohort of 256 probands with FTD were classified according to pattern of family history and screened for pathogenic mutations in the FTD-causing genes.[59, 60] 88% of patients with the strongest autosomal dominant family history were found to carry such mutations. These families were characterized as having at least three affected family members in two generations specifically with FTD, MND or one of the Parkinson's Plus syndromes (CBS or PSP). In addition, one affected person must also be a first-degree relative of the other two affected family members. For the patient group where three or more family members had dementia in general, but not satisfying the above criteria, then 41% were found to have mutations. The probability of finding a mutation for patients with only one family member with dementia depends on the age of onset of the relative. 31% of patients with one relative demented before the age of 65 were found to have mutations. In contrast, only 13% of patients with one relative demented after the age of 65 were found to have mutations. Only 7% of patients without a family history were found to have mutations.

What to test? Genetic testing for families with Mendelian forms of Frontotemporal Dementia
Three causative genes explain over 80% of FTD families with strong autosomal dominant family history[59], namely, Microtubule-associated protein Tau (*MAPT*), Granulin (*GRN*), and Chromosome 9 Open Reading Frame 72 (*C9ORF72*). *MAPT* was the first to be discovered in 1998.[61] It was discovered using a positional cloning approach, among families linked to chromosome 17 presenting with FTD 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. This leads to impaired microtubule assembly/ axonal transport, and can promote pathologic Tau filament aggregation.[62] It was soon realized that a number of other chromosome 17-linked FTD families did not have *MAPT* mutations, and had Ubiquitin rather

than Tau-based histopathology. These families were eventually found to have mutations in the *GRN* gene in 2006.[63, 64] Most mutations in *GRN* are null mutations that lead to nonsense-mediated decay of mutant *GRN* messenger ribonucleic acid (mRNA) and reduced expression of Progranulin (PGRN). Consequently it is possible to identify mutation carriers by measuring serum PGRN levels.[65] Progranulin is a glycoprotein with a range of cellular regulatory functions and its exact role in neurodegeneration is still being investigated.[66] Finally, in 2011, a number of chromosome 9- linked families with FTD/ MND, and Transactive response DNA binding protein-43 (TDP-43) based pathology, were found to be have expanded GGGGCC hexanucleotide repeats in the intronic region of the *C9ORF72* gene.[67, 68] Under 20 repeats is regarded as normal[68], although there are now examples of people with normal cognition and >30 repeats.[69] While the typical pathogenic *C9ORF72* repeat is in the hundreds, the lower limit of the pathogenic range may be as low as 65 repeats.[69] There are families with both mutations in *C9ORF72* and other MND-related genes, suggesting that MND may be oligogenic in nature.[70] The pathogenesis of *C9ORF72*- related FTD is still being elucidated. Function of the *C9ORF72* encoded protein is currently unknown, but the GGCCCC repeats do form nuclear RNA foci in affected cells.[67] This may indicate a shared, RNA-mediated neurodegenerative mechanism, with other noncoding repeat expansion disorders.

All three genes cause disease in an autosomal dominant manner. Mutations in *C9ORF72* tends 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 FTD series found 11·7%, 7·6% and 6·3% of people carrying *C9ORF72*, *GRN* and *MAPT* mutations respectively.[67] *GRN*[71] and *C9ORF72*[72] can be associated with reduced penetrance, and are both found in apparently sporadic cases. Moreover, *C9ORF72* appear to be more common in

familial MND patients of European ancestry (39%) and rarer in comparable East Asian patients (5%).[73]

In addition to the three main FTD-causing genes, there are a number of rarer genetic causes of FTD. Mutations in the chromosome 9 Valosin-Containing Protein (*VCP*) gene cause autosomal dominant FTD together with inclusion-body myositis and Paget's disease of the bone.[74] Mutations in the chromosome 16 Fused in Sarcoma (*FUS*) gene most commonly cause MND without dementia[75] although *FUS* mutations have also been associated with clinical FTD.[76] Interestingly people with FTD and FUS histopathology, tend not to have mutations in the *FUS* gene.[77] Mutations in the chromosome 3 Charged Multivesicular Body protein 2b (*CHMP2B*) gene has been found in a large autosomal-dominant Danish FTD pedigree,[78] but is very rare otherwise. People with *CHMP2B* mutations also have an unusual Ubiquitin positive, but TDP and FUS negative pathology (FTLD-UPS).

Clinical FTD has also been reported for people with mutations in a number of genes typically associated with other diseases. These include the chromosome 2 Dynactin-1 gene,[79] Presenilin-1 gene,[80, 81] and the chromosome 1 Transactive response (TAR)-DNA-binding protein (*TARDBP*) gene.[82]

Genotype-phenotype correlation for the FTD genes has been summarized in two excellent reviews.[57, 83] While there is strict correspondence between causative gene and histopathology, there is much overlap in the relationship between causative gene and clinical presentation, and one may not be able to predict the causative gene based on phenotype alone. For instance, all three of the main FTD genes can cause behavioral variant FTD, or have Parkinsonism as part of the clinical presentation. Our practice is therefore to utilize histopathologic data when available, then prioritise gene testing according to some of the more specific phenotypes associated with each causative gene (Table 2). While the typical FTD/MND family is likely to have a *C9ORF72* mutation, occasionally MND can also be

seen in families with *GRN* mutations.[84] Traditionally, Corticobasal Degeneration (CBD) has been thought to be a Tau-based disease, but a CBD like clinical picture is not uncommon in families with *GRN* mutations.[85] Consequently that constellation of signs and symptoms have been renamed Corticobasal Syndrome (CBS) and we suggest considering both *GRN* and *MAPT* when genetic testing for CBS families. Psychotic symptoms can occur up to 38% of people with *C9ORF72* mutations,[86] but hallucinations can also be part of the presentation for people with *GRN* mutations.[71] A somewhat unique finding in FTD families with *C9ORF72* mutations is cerebellar involvement clinically,[87] by imaging,[88] and in histopathology.[89] This may 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,[88] although there is no easy way to apply this to individual patients in the clinic at present.

Finally, in the absence of pathology data, there can be significant overlap in clinical presentation between AD and FTD.[90] In such cases where the diagnosis is unclear, patients may be advised to have both AD and FTD genes tested.

Advice for the other families

For people with a non-Mendelian family history of FTD, the best information for dementia risk comes from a population-based study in the Netherlands.[91] Using a case-finding approach, Stevens et al. identified and verified all cases of FTD in a population of 15 million. Among the 411 first-degree relatives of people with FTD, the cumulative incidence of dementia before age 80 was 22%. The cumulative incidence was lower (18%), once the Mendelian families with *MAPT* mutations were excluded (*MAPT* was the only FTD causative gene known at the time). This compared to 11% among 2934 first-degree relatives of matched population-based controls. In other words, people with a non-Mendelian family history of FTD have roughly twice the life time risk of dementia compared to the general population, and this increase in risk is similar to that found in relatives of people with AD.

Genetic testing for familial dementia with additional neurologic features

Cognitive impairment is common in neurogenetic conditions, and familial dementia often presents with additional neurologic features. We have summarized some of the more common conditions in Table 3 and Rossor et al. also provides a comprehensive review.[13]

Two conditions deserve a special mention: Huntington Disease and Dementia with Lewy Body Disease. Huntington Disease is one of the most common neurogenetic disorders[92] and can present without chorea (Table 3). It is a particularly important differential for any patient with very early onset dementia (onset age 20s-30s). Dementia with Lewy Bodies (DLB) typically presents in a sporadic manner.[93] However there is a small increase in risk of DLB among siblings of people with DLB, compared to siblings of people with AD,[94] and families with autosomal dominant pattern of inheritance do exist.[95] Dementia is also common in Parkinson Disease (PD),[96] and it is helpful to consider Parkinson Disease Dementia and DLB as diseases in the same 'Lewy Body Disorder' (LBD) spectrum.[97] For the rare LBD families, testing for PD-causing genes[98] should be considered, especially Alpha-Synuclein. Mutations in the Glucocerebrosidase (*GBA*) gene cause the lysosomal storage disease Gaucher Disease in a recessive manner, requiring mutations in both copies of the gene. However in one case series, carriage of one abnormal copy of the *GBA* gene has also been found in 23% of people with pathologically confirmed DLB.[99]

Practical aspects of genetic counseling

Genetic testing can be carried out on a symptomatic or on a predictive basis. Symptomatic testing is for people already diagnosed with dementia, while predictive testing is for people who are clinically well. Genetic counseling is helpful in both situations, but formal

counseling with a geneticist is essential for people undergoing predictive testing. There are now a number of guidelines for genetic testing in AD and FTD. [20, 100]

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 for information-giving to the patient's family members and to offer genetic counseling. Table 4 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 neurologic review may be helpful, especially for the subgroup with memory symptoms. Formal counseling from a clinical geneticist/ genetic counselor is essential. People requesting predictive testing require additional support and information, as there is currently 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[101] and the US Alzheimer's Association.[102] Many individuals at one in two risk, when adequately informed, choose not to proceed with testing.

The principles of predictive testing are well established for Huntington Disease, and the 1994 guideline remains a helpful document.[103] In general, predictive testing is only recommended for adults, and testing should be delayed if there is evidence of significant psychological or psychiatric problems. The testee is encouraged to involve a family member or friend as a support person throughout the testing process. The testee should be aware of the lack of specific preventative interventions if she/he tests positive, and potential harms including psychological harms, and difficult access/exclusion from certain insurance policies. There should be a significant time period between information giving and the final decision to test, and there should also be post-test follow-up counseling. Suicide is a known risk in genetic testing, and the Columbia Suicide Severity Rating Scale is one helpful assessment tool in this

context.[104] If genetic testing is considered in the context of reproductive planning, the possibilities of prenatal genetic testing and pre-implantation diagnosis[105] should be discussed. Finally, individuals identified as unaffected mutation carriers may 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 (http://endalznow.org/) and Dominantly Inherited Alzheimer Network initiatives (http://dian-info.org/).

Conclusions

Dementia is a common condition and family history of dementia is also common. Fortunately Mendelian forms of dementia are rare. This means that for relatives of most people with dementia, their life-time risk of dementia is around 20%, compared to about 10% in the general population. However, in the small proportion of families where 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 or 1 in 2 chance of inheriting the mutation, and with the mutation, a lifetime dementia risk of over 90%.

In this review we have highlighted the importance of a detailed family history, and clinical clues to help clinicians prioritise which gene(s) to test first. At the time of writing, the field of genomic analysis in human inherited disease is undergoing a process of 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 noncoding regions, for the human genome in one test)[106] 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

conditions where the there are multiple causative genes with overlapping phenotypes, such as FTD, and remove 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, for a patient with clinical AD.[107] There are already examples of successful genetic diagnosis using these techniques.[108, 109] While these techniques still require validation before routine clinical use, and will generate new clinical and ethical dilemma[110] (eg. interpretation of rare and novel variants), they will revolutionize the way we think about genetic testing and bring us closer to the ideal of personalized medicine.

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TABLE 1

Probability of finding a pathogenic mutation in one of the recognized Alzheimer Disease genes, among multiplex families

Pattern of inheritance	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	<61years	68%
Two or more affected, first degree relatives	<65years	15%
Two or more affected, first degree relatives	>65years	<1%

Legend: see main text for detailed explanation and references.

TABLE 2

Clinical clues which may help prioritise genetic testing in familial FTD

Clinical clue	Suggestions for priortised genetic testing[1,2]
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, GRN*
Highly variable age of onset or reduced penetrance	*GRN, C9ORF72*
Cerebellar involvement	*C9ORF72*
Other associations	Inclusion Body Myositis/ Paget's Disease of the Bone (*VCP*), Danish ancestry (*CHMP2B*)

1. Genetic testing may proceed to other genes if the suggested genes are normal/negative

2. See main text and Panel 1 for full names of abbreviations, and detailed explanations of the genetic and histopathologic subtypes

TABLE 3

Genetic testing for familial dementia with additional neurologic features

Clinical presentation	Gene(s) to consider	Comments
Dementia with myoclonus	Prion (*PRNP*) gene[111]	Genetic Prion disease has three clinical subtypes: Familial Cruetzfeldt- Jakob disease, Gerstmann-Straussler-Scheinker disease, and Fatal Familial Insomnia- with some genotype-phenotype correlation.[112] Rarely mutations in the PRNP gene can also produce progressive memory loss similar to AD.[113, 114]
	AD-causing genes	Myoclonus can also present as an early feature in familial AD.[115]
Dementia with chorea	Huntingtin (*HTT*) gene[116]	People with Huntington Disease may not present with chorea as the first symptom. Cognitive impairment can precede chorea for decades,[117] and the Westphal variant is characterized by rigidity rather than chorea.[118]
	Genes causing Huntington-like phenotype	These include genes causing Spinocerebellar Ataxia Type 3, Spinocerebellar Ataxia Type17, Dentatorubropallidolysian Atrophy, Neuro-acanthocytosis, Neuroferritinopathy, & Junctophilin-3 mutations.[119, 120]

Dementia with ataxia	Genes causing cerebellar ataxia[121, 122]	Examples of genetic forms of ataxia with cognitive impairment include: Spinocerebellar Ataxia Type 2, [123] Spinocerebellar Ataxia Type 3,[124] Spinocerebellar Ataxia Type 17,[125] DRPLA,[126] and neuroacanthocytosis . This list is likely to grow.
Dementia with dystonia	ATPase-7b (*ATP7B*) gene for Wilson Disease[127, 128]	Wilson Disease is Autosomal Recessive so there may not be a family history. Nonetheless it is an important differential as it is potentially treatable.[129]
	Niemann-Pick Disease Type C1 (*NPC1*) and Niemann-Pick Disease Type C2 (*NPC2*) genes	Niemann-Pick Disease Type C is an autosomal recessive lysosomal lipid storage disease, which sometimes presents in young adulthood with a spectrum of clinical findings including cognitive impairment, supranuclear ophthalmoplegia, dystonia, ataxia, and splenomegaly.[130] It is diagnosed by biochemical testing of fibroblast culture or genetic testing, and is potentially treatable.[131]
Dementia with white matter changes on imaging	Genes causing paediatric white matter diseases[132]	This in a young adult raises the possibility of metabolic, mitochondrial and other inherited disorders. Differential is broad but serum

		lactate, serum amino acid, urinary organic acids, and consult with a metabolic physician would be a good starting point.
	NOTCH 3 (*NOTCH3*) gene[133]	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant condition with migraines, young onset strokes, dementia and white matter changes on MRI.[134] 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 2 per 100,000.[135]
Dementia with progressive myoclonic epilepsy (PME)	Specific genes for each disease causing PME[136, 137]	This is a heterogeneous group of disorders, which include: Myoclonus epilepsy and ragged red fibres, Unverricht-Lundborg Disease, Lafora Body Disease, Neuronal Ceroid Lipofuscinoses, and Type I Sialidosis. In the past diagnosis had required tissue biopsies but the causative genes have now been found for many of these disorders.

TABLE 4

Information for patients, when considering molecular genetic testing for an autosomal dominant disorder

1. We have approximated 25000 genes each, and a fault in any one of these can be sufficient to cause disease.

2. We have two copies of each nuclear encoded gene, one from each parent.

3. In 'autosomal dominant' conditions, a mistake in one of the two copies of a gene, is sufficient to cause disease.

4. In autosomal dominant dementia, an affected person carries one faulty copy of a dementia gene, as well as a normal copy of that gene.

5. Each offspring of the affected parent will therefore have a one in two, or 50:50 chance of inheriting the faulty copy of the gene, and a one in two, or 50:50 chance of inheriting a normal copy of the gene. These probabilities apply to each offspring, regardless of the gene status of her/his brothers or sisters. Each offspring will also inherit a normal copy of the gene from the unaffected parent.

6. An offspring who has inherited the faulty copy of a dementia-causing gene, is highly likely to develop this form of dementia within her/his lifetime, as these faults tend to be of 'high penetrance'. However the genetic test does not predict age of onset. Her/his children will also have the one in two, or 50:50, chance of inheriting the faulty copy of the gene.

7. An offspring that has not inherited the faulty copy of the dementia-causing gene, will not develop this form of dementia, and neither will her/his offspring.

PANEL 1

Frontotemporal Dementia (FTD)

Clinically, FTD is a heterogeneous group of syndromes characterized by progressive deterioration in behavior, speech production or language, with relative sparing of memory and visuospatial function. FTD can be subdivided into three clinical subtypes: behavioral variant FTD (bvFTD), Progressive Non-Fluent Aphasia (PNFA) and Semantic Dementia (SD). PNFA and SD are sometimes grouped together under the umbrella term Primary Progressive Aphasia (PPA). The Neary criteria[52] remains a helpful description of the FTD clinical subtypes. However, there is a revised criteria for bvFTD which is likely to improve the sensitivity and specificity of clinical diagnosis.[138] This incorporates 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 PPA- the logopenic variant,[139] which is characterized 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 appears to be distinct from PNFA and SD, although only a small proportion of non-PNFA and non-SD patients fits into this subtype.[140] Generally speaking, these clinical subtypes correlate well with specific imaging findings.[54] (Figure 3)

Clinical subtypes also correlate with specific histopathologic subtypes to a certain degree- although clinical prediction of underlying histopathology is not straight forward. The nomenclature of histopathologic subtype of frontotemporal lobar degeneration (FTLD) was updated in 2010.[141] FTLD histopathologic subtypes are classified according to immunohistochemical reactivity to a number of proteins, including: tau (FTLD-tau), Transactive response DNA binding protein-43 (FTLD-TDP), and Fused in sarcoma protein (FTLD-FUS). Prior to discovery of the roles of TDP and FUS in FTLD, FTLD-TDP and FTLD-FUS were both classified under '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-UPS (Ubiquitin Proteosome System). Semantic Dementia has the most consistent underlying histopathology- 75% of cases in a histopathologic series were found to have FTLD-U, and the retrievable cases were all TDP positive.[142] Histopathology is much more variable for bvFTD (can be any of the FTLD subtypes) and PNFA (FTLD-tau or FTLD-TDP). It should also be noted that these clinical subtypes are not 100% specific for FTLD either, and other neurodegenerative diseases such as Alzheimer Disease may also mimic FTD, PNFA and SD clinically. Other clues for clinico-histopathologic correlation include: FTD associated with motor neuron disease is associated with FTLD-TDP,[143] and very early age of onset without a family history may predict FTLD-FUS.[144]

The relationship between genetic mutations and histopathology is more straight forward. In general, mutations in a specific gene only lead to one histopathologic subtype (Table 2). Histopathologic diagnosis in a family member will remove the uncertainty of predicting histopathologic subtype based on clinical phenotyping alone, and is invaluable in genetic studies.

FIGURE LEGENDS

Figure 1

Pathogenesis in Mendelian versus Complex disease. In a Mendelian disease, mutation in a single gene is necessary and sufficient to cause disease. In a Complex disease, normal variation in multiple genes interact with the environment to increase disease risk.

Figure 2

The Amyloid Hypothesis and pathogenesis in Alzheimer Disease. All three of the AD-causing genes are involved in Amyloid-β production, although other factors are likely to also play a role in the pathogenesis of Alzheimer Disease in general. *APP*= Amyloid Precursor Protein , *PSEN1*=Presenilin-1 , *PSEN2*= Presenilin-2

Figure 3

Frontotemporal dementia (FTD) is a group of disorders characterised by degeneration of the frontal and/or temporal lobes, but is heterogeneous in clinical presentation, imaging features, underlying histopathologic subtypes, and genetics among the Mendelian families.

Legend: FTLD= Frontotemporal Lobar Degeneration, TDP= Transactive response DNA binding protein-43, FUS= Fused in sarcoma protein, UPS= Ubiquitin Proteosome System

SEARCH STRATEGY AND SELECTION CRITERIA

We searched MEDLINE (1946-Feb2013) using the OvidSP platform. A typical search uses explode and textword functions. For example, genetics of frontotemporal dementia was searched using the strategy (exp Frontotemporal Dementia/ OR frontotemp$.tw) AND (exp genetics/ OR (gene OR genes OR genet$).tw). Further studies were identified by searching reference lists of review articles, and by searching Web of Science to identify studies citing seminal papers. Studies were chosen for their currency, scientific merit/study design and sample size. If there are multiple studies with the same observation we chose the first definitive study.

AUTHORS' CONTRIBUTIONS

All authors contributed to the writing and reviewing of this paper.

CONFLICT OF INTEREST

There are no conflicts of interest.

ETHICS COMMITTEE APPROVAL

Not required.

Single Gene (Mendelian) Disease

X

Gene Mutation

Disease

Complex Disease

Environment

Environment X Gene

Gene Variant 1

Gene Variant 2

Disease
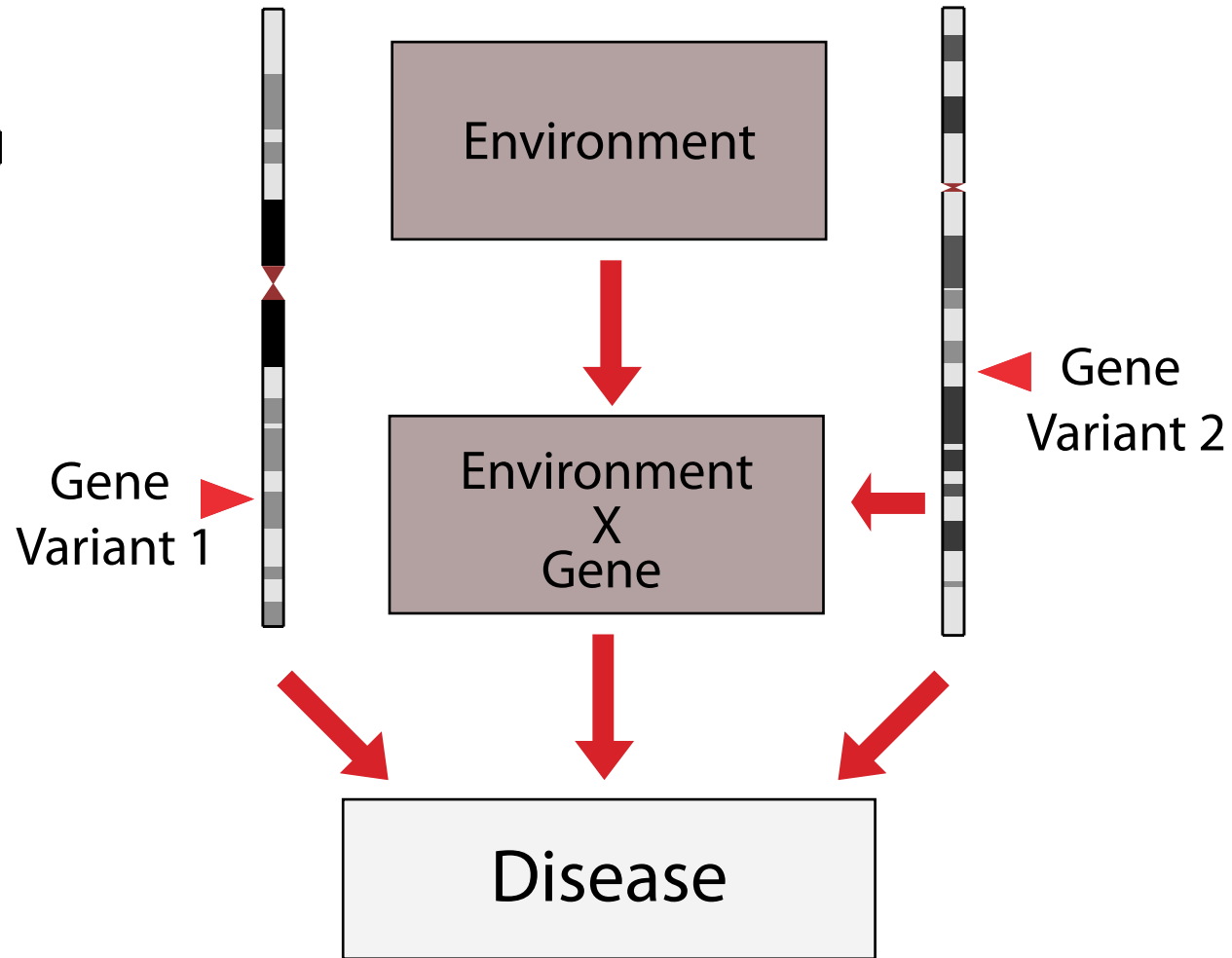
Normal Protein Degradation

APP
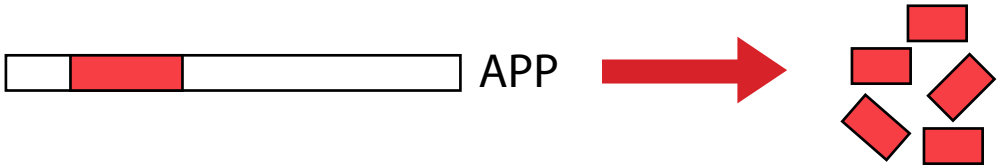
Down Syndrome
(*APP* Duplication)

APP

APP
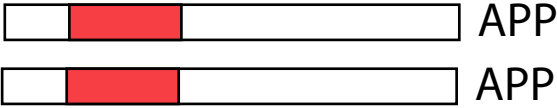
APP mutation
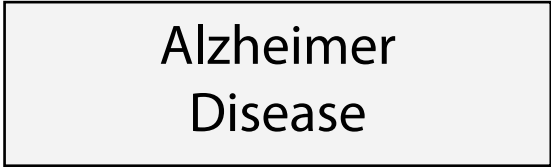*PSEN1,PSEN2* mutations

Increased β-Amyloid
Production

Tau Hyperphosphorylation
and Tangles
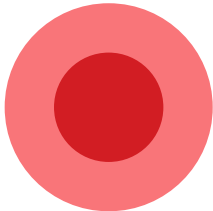
Plaque Formation

Cell Death

Alzheimer
Disease

Aetiology	Histopathology	Imaging	Clinical presentation

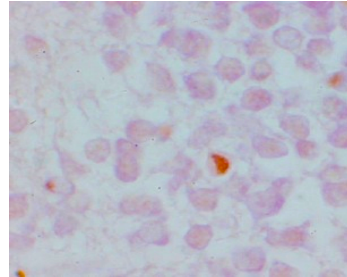**Aetiology**

MAPT gene

GRN gene

C9ORF72 gene

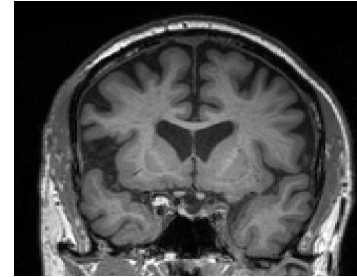Other
Mendelian
genes

Other genetic/
Environment?

Histopathology

FTLD-tau
FTLD-TDP
FTLD-FUS
FTLD-UPS

Imaging

Different patterns of
atrophy
- Fronto/temporal
- Left Perisylvian
  (Progressive
   Non-Fluent
   Aphasia)
- Left anterior temporal
  (Semantic Dementia)

Clinical presentation

Behavioral variant FTD

Language variant FTD

  - Progressive Non-
    Fluent Aphasia

  -Semantic Dementia

  -Logopenic variant

 +/-
Motor Neuron Disease
Parkinson-plus Syndromes
Inclusion Body Myositis