Chapter 12
Genetic testing

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Key points

- A structured genetic assessment is required if there is a suspicion of familial type of dementia.
- Genetic assessments should be conducted by a specialised team able to manage all the medical, ethical and social complexities associated with genetic testing.
- Although APOE4 is the major genetic risk factor for Alzheimer’s disease, APOE4 genotyping is not currently recommended in routine clinical practice.
- Access to genetic assessment constitutes a major challenge in low- and middle-income countries.
General background

The risk of developing dementias such as Alzheimer’s disease, Lewy body or frontotemporal dementias may be dependent on certain genes. These genes can either cause, protect or increase the risk of developing dementia. When several members of a family have been previously affected by dementia, an individual should be carefully assessed by healthcare professionals to determine whether a genetic component runs in their family and may increase their chances of developing the condition. As such, doctors will select the appropriate tests to order, interpret the findings, and share the results with the individuals concerned.
Survey results

17% of the multidisciplinary clinicians who participated in the survey indicated that they have access to genetic testing in accordance with national guidelines while 39% indicated that genetic testing is performed based on clinical grounds. While genetic testing is not available to 35% of the participants, 33% had limited access. Low- and middle-income countries have less accessibility (Chart 1).

Do you order genetic testing (such as APOE, screening for autosomal dominant mutations of PS1, PS2, APP, polygenic risk score) for people concerned about their cognition?

Chart 1: Clinician responses.
Genetic testing

The risk associated with developing dementia is often discussed with the children of people with dementia or members from families with a high rate of dementia. However, only in specific cases, do genetic assessments become an important consideration for the person and their family members. Genetic assessment searches for defects in genes that causes brain accumulation of amyloid, tau, alpha-synuclein, transactive response DNA binding protein 43 kD (TDP-43) and other pathogenic proteins. When well indicated, genetic testing offers a precise molecular diagnosis and guides family members to determine their own personal risk, provides a basis for reproductive choices and offers options for clinical trials (1).

When is genetic assessment of dementia patients needed?

Most dementia cases are caused by illnesses in which a certain pool of genes might confer vulnerability to disease pathophysiology. However, in a small percentage of cases, dementias are caused by rare mutations, or copy number variants, or repeat expansions. While some of these cases may be recessive, others show an autosomal dominant pattern. At primary care, family history plays an important role in identifying those individuals with a high number of affected family members, particularly at a young age. While recording the family history, one should take into consideration multiple phenotypes within a family (namely, frontotemporal dementia and motoneuron diseases or progressive aphasia). Families with a high frequency of young-onset or atypical dementias should be assessed by a multidisciplinary team capable of handling the complexities associated with the diagnostic procedures, disclosure, counselling, and management of these families. Such an assessment should include cognitive testing, neurological examination and a multi-generation family history able to estimate the likelihood of an autosomal dominant trait (that is, the Goldman criteria) (2).

Genes associated with sporadic Alzheimer’s disease

By far, the most important genetic risk factor for dementia due to Alzheimer’s disease is the apolipoprotein ε4 gene. The apolipoprotein gene, located on chromosome 19, has three polymorphisms called ε2, ε3, and ε4. They code for a protein involved in brain cholesterol, which plays a role in brain repair. Carriers of the ε4 allele have a higher risk of developing dementia due to Alzheimer’s disease. This common variant is present in up to 30% of the population. In fact, 40–65% of people with dementia due to Alzheimer’s disease have at least one ε4 allele. The risk associated with a single ε4 allele is especially prominent in women and increases in double ε4 carriers. However, it is important to emphasise that carrying the ε4 genotype is neither necessary nor sufficient to cause dementia. For this reason, apolipoprotein ε testing is not clinically useful. Interestingly, the ε4 allele is not associated with risk for frontotemporal dementia, dementia with Lewy bodies, or Creutzfeldt-Jakob disease (3–5).

Research conducted in Alzheimer’s disease using genome-wide association designs identify a wide range of common gene variants involved in lipid metabolism, endocytosis, vesicle recycling and neuroinflammatory responses. It has been proposed that the risk of developing dementia is higher in carriers with certain polygenic gene signatures (6–8).

Down syndrome

Down syndrome (trisomy 21) is a common form of young-onset dementia. Adults with Down syndrome, after the age of 40, consistently show a progressive cognitive decline and dementia superimposed on their baseline cognitive limitations. They accumulate amyloid, neurofibrillary tangles and cell depletion similarly to sporadic Alzheimer’s disease. Due to the trisomy of the chromosome 21, these individuals carry an extra copy of the amyloid precursor protein, which is believed to be responsible for dementia in adults with Down syndrome (9, 10).

Genes associated with autosomal dominant Alzheimer’s disease

Three causative genes have been associated with autosomal dominant familial Alzheimer’s disease. Mutations in the APP, presenilin-1 (PS-1; chromosome 14) and presenilin-2 (PS-2; chromosome 1) code for proteins involved in β42 production pathways, which is a toxic component of amyloid plaques. PS-1 mutations account for most autosomal dominant cases. Autosomal dominant Alzheimer’s disease has an earlier dementia onset and progresses more rapidly than sporadic cases. Depending on the location, mutations phenotypes might vary from typical dementia to more complex presentations, featuring motor symptoms or behavioural abnormalities. Individuals with a high number of affected family members with young-onset should undergo specialised clinical assessment and genetic testing for rare variants. Research conducted within the Colombian PS-1 E280A kindred, and the Dominantly Inherited Alzheimer Network (DIAN) have tremendously advanced the understanding of Alzheimer’s disease based on research conducted in autosomal dominant families. A brief summary of these genes is listed in Table 1 (11–22).
Protective genes in Alzheimer's disease

Interestingly, there are genes that provide resilience to dementia. For example, the Icelandic APP coding mutation (A673T) protects against Alzheimer’s disease and cognitive decline in the elderly. APOE2 allele has one of the strongest genetic protective effects according to genome-wide association meta-analyses. The rare apolipoprotein ε3 mutation called Christchurch, when in homozygosis, seems to protect against dementia despite the presence of a PS1 mutation. A genetic variant in the PLCG2 gene reduces the risk of Alzheimer’s disease and other neurodegenerative conditions (23–26).

Genes associated with frontotemporal dementia

Frontotemporal dementia cases require a careful assessment of family history. Up to 50% of frontotemporal dementia patients have a positive family history of dementia or psychiatric conditions. Careful clinical assessments identify an autosomal dominant pattern in up to 15% of cases. Indeed, individuals with the association between behavioural variant frontotemporal and motor neuron disease, are most likely to carry genetic alterations. Frequent causal genes associated with frontotemporal dementia are summarised in Table 1. MAPT and progranulin mutations in addition to the C9ORF72 hexanucleotide are the three genetic abnormalities responsible for 15% of familial frontotemporal dementia cases (2, 27, 28). Mutations in the MAP-T gene or progranulin gene mutations located in chromosome 17 will cause protein aggregations within the neurons leading to cell death and dementia. In chromosome 9, a six-nucleotide repeat expansion on the C9ORF72 gene is the most common genetic cause of familial FTD and familial amyotrophic lateral sclerosis (ALS) (29–31).

Other genes associated with dementia

Many people with genetic diseases may present dementia as part of their clinical phenotype. Apart from the Alzheimer’s disease related conditions, family prion diseases, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), Huntington’s disease, Wilson’s disease, dentatorubropallidoluysian atrophy, Niemann Pick type C, spinocerebellar ataxias are examples of genetic conditions frequently associated with dementia (32).

Table 1. Genetic abnormalities associated with neurodegenerative dementias

<table>
<thead>
<tr>
<th>Genes</th>
<th>Name</th>
<th>Chromosome</th>
<th>Mutations</th>
<th>Repeats</th>
<th>Dementia type</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS1</td>
<td>Presenilin 2</td>
<td>14</td>
<td>326</td>
<td></td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
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<td>Presenilin 2</td>
<td>1</td>
<td>68</td>
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<td>APP</td>
<td>Amyloid precursor protein</td>
<td>21</td>
<td>69</td>
<td></td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>M1AP</td>
<td>Microtubule associated</td>
<td>17</td>
<td>63</td>
<td></td>
<td>Frontotemporal dementia</td>
</tr>
<tr>
<td></td>
<td>protein tau</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRN</td>
<td>Pro-granulin gene</td>
<td>17</td>
<td>114</td>
<td>&gt;30</td>
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</tr>
<tr>
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<td>9</td>
<td>15</td>
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<td>VCP</td>
<td>Fuse in Sarcoma</td>
<td>16</td>
<td>2</td>
<td></td>
<td>Familial ALS</td>
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The last 30 years paved the way and cemented the immense role genetics play in our understanding of Alzheimer’s disease. Two different aspects should be distinguished. The autosomal dominant inheritance, which is extremely rare but has a complete risk of inducing illness before the age of 65 for all carriers of a causative mutation. In parallel, there are many genetic risk factors that can lead to a high but not complete risk, such as the e4 genotype of the APOE gene, common in the general population, or others that are much less frequent, such as the TREM2, SORL1 or ABCA7 genes. Finally, more than twenty frequent polymorphisms have been found to be related to Alzheimer’s disease but weakly associated with its occurrence.

The so-called ‘hereditary’ or autosomal dominant forms of Alzheimer’s disease

For a minority of people, representing less than 1%, Alzheimer’s disease is due to a causal mutation in one of these three genes: APP, PSEN1 or PSEN2. These mutations lead to an early-onset of Alzheimer’s disease beginning before the age of 65 with affected relatives from generation to generation and both men and women. This explains why these mutations are typically found in families with early-onset Alzheimer’s disease. About 80% of them are linked to a mutation within PSEN1, APP or PSEN2 (1). Any individual carrying one of these mutations will develop symptoms before 65 and approximately at the same age of their own parent. Historically, APP was the first gene to be identified (2) but PSEN1 represents the major gene in proportion of families (43%). Since 2006, increases in APP copy number or APP duplications have been reported as causative with a clinical phenotype close to point mutations of the same gene (3). Mutations and duplications of APP represent 9% and 7% respectively. Finally, the third gene identified to date is PSEN2, but it concerns only a small minority of families (6%) (1). The phenotypes described are mostly typical forms with memory disorders (80% of cases). Depending on the gene, the ages of onset range, on average, from 43 years for PSEN1 to 53 years for PSEN2 (4,5) but in some rare cases, some were reported with a very young age of onset as 24 years old. Several atypical situations are also encountered, particularly for certain PSEN1 or APP mutations (4–6): behavioural modifications (9% of patients) and non-cognitive manifestations such as early epileptic seizures (7), spastic paraparesis for 9% (1,6). Sporadic cases are also reported harbouring a mutation in one of these three genes. One explanation is the occurrence of a de novo mutation (8). This underlines why it is preferable to talk about autosomal dominant forms rather than ‘familial’. Some countries, such as France, have published criteria for the genetic diagnosis based on this clinical data. Indeed, a genetic analysis should be proposed in people with early-onset Alzheimer’s disease, beginning at 65 years of age or before, if there is at least one other relative with a family history with early-onset Alzheimer’s disease. For sporadic cases, people with an age of onset before 51 years should also qualify for a molecular diagnosis (9).

Genetic risk factors

Apart from these rare situations, the other forms of Alzheimer’s disease, whether early or late, familial or sporadic, are part of a complex framework with significant genetic heterogeneity. The explanatory part related to either genetic or environmental components has been highly debated but twin studies have demonstrated the important genetic component (10). The APOE gene coding for apolipoprotein E (APOE) has been identified since the end of the 1980s and in particular the impact of the e4 allele found in about 21% of the general population (11). The increased risk of Alzheimer’s disease related to the presence of this allele was moderate to high, depending on whether the individual was carrying one or two e4 alleles. Subsequently, technological developments have, since 2000, allowed further genetic research. Indeed, thanks to DNA chip techniques capable of searching for the presence of genetic variations in large international cohorts of patients, these genome-wide association studies compare the DNA of tens of thousands of patients and controls to identify frequent variants (12). Several dozen genetic
polymorphisms, for instance linked to PICALM or BIN1, have been identified as being associated with Alzheimer’s disease, but with a risk considered to be low. That risk has therefore a limited interest in the management of patients but allows to study some mechanisms of the disease.

In parallel to these genome-wide association studies, next generation sequencing (NGS) appeared in the late 2000s. The goal of these methods is to uncover all the variants present in the genome of each individual. Applied to Alzheimer’s disease research, that technique makes it possible to identify all the variants present on the coding parts of our 20,000 genes by whole-exome sequencing (WES) and to identify those present in patients and absent in healthy controls, or conversely. This method, without any presumption about the gene to be identified, offers the advantage of being able to look at variants regardless of their frequency, even low (<1% of the general population) or very low (<0.1%) frequencies. These strategies allow researchers to manage a huge amount of data and to establish specific methods to restrict the number of potential candidates related with Alzheimer’s disease. Rare variants identified within TREM2, SORL1, and ABCA7 genes are known to explain between 1.1% and 1.5% of early-onset Alzheimer’s disease heritability each, as compared to 9.12% for APOE4 (13).

Clinical and ethical consequences

Distinguishing between genetic variants within causative genes for the ‘hereditary’ forms, or just risk factors, is not only a question of classification. This has consequences in terms of research and clinical practice for individuals and their families. Indeed, the causative mutations of PSEN1, PSEN2 and APP are responsible for an almost complete probability of becoming ill before the age of 65. This point justifies providing well-defined information to families for which first-degree relatives are at high risk (in practice, 50% for each individual) of carrying the same mutation and therefore becoming ill. This information is most often provided, as in France or Canada, by the genetic counsellor. If the multidisciplinary process is completed, the person requesting it will be able to obtain a presymptomatic diagnosis, in other words, to know their genetic status before the onset of Alzheimer’s disease symptoms. These rare forms of the disease have allowed for the implementation of research protocols specifically dedicated to improving our knowledge of the disease. Since 2013, it has been possible to include asymptomatic relatives to receive experimental treatment aimed at preventing or delaying the onset of Alzheimer’s disease, such as the DIAN-TU protocol (14). Unfortunately, the primary criteria, based on clinical efficacy was not met, but the study is being pursued with an open label extension to get more information on a long-term impact of the treatment (15).

The situation of genetic risk factors is quite different. Indeed, by definition, a risk factor is neither necessary nor sufficient for the disease but only modifies the risk at a given age. In other words, the risk associated with carrying 2 APOE4 alleles cannot justify a presymptomatic diagnosis, even if the attributed risk is high. That situation could change in the next few years if preventive therapeutic research protocols based on the presence of a risk factor are positive. A programme led by the Banner Alzheimer Institute is aiming to meet this objective with specific ethical procedure regarding APOE genotype disclosure (16). In the meantime, the problem remains the same for all risk factors, whether they are rare or frequent. None can justify a presymptomatic diagnosis, but it is important to continue investigations in these families to determine a potential additive or even synergistic effect of these variations in a given individual. To meet that goal, several research teams are working on determining polygenic scores or age-related risk curves (12,17). This personalisation of the risk for Alzheimer’s disease should overcome the significant genetic heterogeneity and to propose an effective and personalised therapeutic strategy, particularly critical for prevention.
References


As that person, I find myself learning the art of losing every day. Losing my bearings, losing objects, losing sleep. But mostly, losing memories.' It’s a classic line from the movie Still Alice, about a linguistics professor who struggles to maintain her mind and self after being diagnosed with familial early-onset Alzheimer’s disease, in autosomal dominant form of inheritance. The movie, based on a true story, can help us understand autosomal dominant Alzheimer’s disease (ADAD), a rare, characteristic, and clinically significant form of Alzheimer’s disease (AD) more clearly.

As depicted on screen, autosomal dominant Alzheimer’s disease is characterised by early-onset cognitive impairment (typically occurring from the ages of 30 to 50), fairly consistent within a family and principally caused by highly penetrant pathogenic mutations in the amyloid precursor protein gene (APP), presenilin 1 gene (PSEN1) and presenilin 2 gene (PSEN2) (1). To date, 326 PSEN1, 68 PSEN2, and 69 APP mutations have been identified, as well as new mutations constantly being discovered in Alzheimer’s disease with a positive or negative family history (2). Dissimilar to the previously held view that all individuals with autosomal dominant Alzheimer’s disease have an explicit positive family history, cases of individuals with autosomal dominant Alzheimer’s disease whose cause is identified as de novo mutation with a negative family history have increased in recent years, and a diagnostic approach of young-onset dementia with negative family history have been proposed (3). Although this occurrence only accounts for 10% to 15% of familial early-onset dementia with negative family history have been proposed (3). Although this occurrence only accounts for 10% to 15% of Alzheimer’s disease cases, autosomal dominant Alzheimer’s disease represents an ideal population to explore pathogenesis, prevention and treatment of Alzheimer’s disease, widely approached by researchers as an independent area of study.

In 2008, the Dominantly Inherited Alzheimer Network (DIAN) an international research organisation focused on autosomal dominant Alzheimer’s disease was established. DIAN, led by Randall Bateman at the Washington University School of Medicine, and represented by several institutions around the world, is dedicated to clinical trials and observational study, as well as working directly with individuals and families who are impacted by autosomal dominant Alzheimer’s disease. Participation by individuals with autosomal dominant Alzheimer’s disease and their families will contribute to the global understanding of how it can be prevented, diagnosed and treated by registering with the DIAN Expanded Registry, as well as help researchers pursue avenues to prevent or minimise its medical and social impact. Among many prominent research achievements based on DIAN, the latest discovery of novel disease trajectories for autosomal dominant Alzheimer’s disease through Machine learning models will contribute to targeted treatment of autosomal dominant Alzheimer’s disease individuals in particular (4).

With the exception of the Dominantly Inherited Alzheimer Network study, research into the world’s largest single-mutation autosomal dominant Alzheimer’s disease kindred, a family in Antioquia, Colombia with the E280A (Glu280Ala) mutation in the Presenilin1 gene, also provided great insight into this disease (5). The autosomal dominant Alzheimer’s disease kindred were first reported in 1997, including approximately 6,000 living members and an estimated 1,200 mutation carriers now. There have been dozens of original articles published based on this Colombia cohort, and the latest comprehensive review unifies the knowledge gained from the past three decades, showing significant abnormalities in plasma, cerebrospinal fluid, brain structure and function as well as evidence of Alzheimer’s disease pathology in as early as three and a half decades before the median age of onset of Alzheimer’s disease-related cognitive decline (6) (Figure 1). We believe more research disclosures will be made from this unique kindred model.

As a hereditary disease, the diversity of autosomal dominant Alzheimer’s disease among different ethnic groups needs to be fully appreciated. Although most of the large-scale autosomal dominant Alzheimer’s disease studies were conducted with Caucasians, some significant original studies have recently been published in Asia, indicating the heterogeneity in the pathogenesis of Alzheimer’s disease between....
different ethnicities. In 2002, the Chinese Familial Alzheimer’s Disease Network (CFAN) was established by director Jianping Jia, Xuanwu Hospital, Capital Medical University. They recruited 404 familial Alzheimer’s disease pedigrees from among 1,330 individuals from 69 medical centres in 26 provinces and regions of China, becoming the largest familial Alzheimer’s disease registration website to date. Through follow-up studies conducted for the past 17 years, a relatively low detection rate of PSENs/APP mutations in Chinese familial Alzheimer’s disease than other ethnic groups was found, suggesting the involvement of other factors such as APOE4, recessive inheritance, incomplete penetrance and de novo mutation in Chinese familial Alzheimer’s disease (7).

Although more and more research advancements in pathogenesis and treatment of Alzheimer’s disease have been made, it would appear there is still an insurmountable gap between delaying the course of the disease and a complete cure. No matter where people are located or their ethnic background, individuals with autosomal dominant Alzheimer’s disease places an even greater emotional and economic burden on families and society as a whole than typical Alzheimer’s disease. For these individuals and their families, reconciling the impact of the disease with learning how to have a beneficial post diagnosis journey are the most important thing. ‘I have people I love dearly. I have things I want to do with my life. I rail against myself for not being able to remember things. But I still have moments in the day of pure happiness and joy. And please, do not think I am suffering. I am not suffering. I am struggling. Struggling to be part of things, to stay connected to whom I once was. So ‘live in the moment’, I tell myself.’ says Alice towards the end of the movie. We sincerely hope that every person with autosomal dominant Alzheimer’s disease and their families continue this struggle, as do the clinicians and researchers who remain dedicated to struggle to do what they can to prevent and treat Alzheimer’s disease.

**Figure 1. Hypothetical Model of Progression of Biological Markers of PSEN1 E280A Autosomal Dominant Alzheimer’s Disease Relative to Earliest Known Signal of Cognitive Decline.**

[https://www.clinicaltrials.gov/ct2/show/NCT03657732](https://www.clinicaltrials.gov/ct2/show/NCT03657732)
References


Frontotemporal degeneration (FTD) is one of the most common forms of dementia in individuals under the age of 65, following Alzheimer’s disease and is characterised by a broad range of different clinical phenotypes. These include progressive changes in personality, behaviour and/or language resulting from underlying neurodegeneration of the frontal and temporal lobes of the cerebral cortex. As these character changes increasingly progress and manifest in inappropriate emotional and behavioural displays in public, its diagnosis remains difficult, with individuals being erroneously diagnosed with psychiatric disorders. People with frontotemporal degeneration may also develop motor deficits, either amyotrophic lateral sclerosis (FTD-ALS) or parkinsonism, in the latter case often with specific features of a corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP). Frontotemporal degeneration is a highly heritable disorder but almost uniquely within the neurodegenerative disease spectrum, it is neither purely genetic (like Huntington’s disease) nor a mainly sporadic condition (like Alzheimer’s disease). It was once thought that the prevalence of variants (4.9–7.7%) was comparatively lower in the Chinese frontotemporal degeneration population (1–4). More recently, individuals diagnosed with bvFTD, which is the most common subtype of frontotemporal degeneration, present with a family history of dementia or other neurodegenerative diseases (28.6% of cases). It has been estimated that 27.9% of frontotemporal degeneration is inherited in an autosomal dominant manner (5). All of these factors highlight the importance of genetics in the aetiology of frontotemporal degeneration in China.

Gene

So far, thirty-eight rare variants in genes of MAPT, GRN, C9orf72, CHCHD10, VCP, FUS and TBK1 were identified in Chinese frontotemporal degeneration populations. The majority of the heritability of frontotemporal degeneration is accounted for by autosomal dominant mutations in three genes: microtubule-associated protein tau (MAPT), progranulin (GRN) and chromosome 9 open reading frame 72 (C9orf72). MAPT (3.9–20.9%) seems to be the most common Chinese cause of genetic frontotemporal degeneration, while the frequency of C9orf72 repeat expansions were comparatively low (1–7). To date, 11 pathogenic variants in MAPT and 4 pathogenic variants in GRN have been currently described in Chinese individuals, most of which are missense mutations (1). N279K and P301L mutations in exon 10 of the MAPT gene are common pathogenic mutations resulting in frontotemporal degeneration in China [1]. C9ORF72 repeat expansion is rare in Chinese FTD-ALS individuals, 1.2–2.1% in frontotemporal degeneration individuals, and 0.8% in ALS patients (1,6–10). In contrast to the relative scarcity of C9ORF72 hexanucleotide expansions, pathogenic mutations in CHCHD10 may be quite common, accounting for 7.7% of frontotemporal degeneration cases in the reported Chinese cohort (3,11,12). Although 12 pathogenic variants in CHCHD10 have been identified, the pathogenic nature of them remains unclear. Further studies are needed for a reliable estimate of pathogenic CHCHD10 mutation prevalence in Chinese frontotemporal degeneration populations. Additional rare genetic causes of frontotemporal degeneration, including 8 pathogenic variants in VCP, TBK1, FUS, ANXA11 and CHCHD2 were also reported in the years following the discoveries of pathogenic variation in MAPT, GRN and C9ORF72. However, these mutations collectively account for only a fraction (<2%) of Chinese patients with FTD (1,13–19).

Phenotype

The most common clinical presentation of all genetic forms is behavioural variant frontotemporal dementia (bvFTD), but all phenotypes within the frontotemporal degeneration spectrum are observed in Chinese frontotemporal degeneration individuals. A variety of phenotypes with MAPT mutation were observed, which to some extent, was associated with mutation location (2–4,21). There were eleven variants reported in Chinese frontotemporal degeneration populations, including N279K, P301L, G389R, R5H, D177V, H299Y, V337M, N296N R5C, D54N and P513A [1]. Early parkinsonism is the common manifestation in individuals with N279K mutation [20]. P301L, MAPT mutation mainly presented with cognitive and behavioural manifestations. Interestingly, one of four affected individuals in the pedigree with P301L mutation presented with parkinsonism and demonstrated the phenotypic variability...
associated with the P301L mutation in individuals with the same MAPT mutation, even within the same family (5). Furthermore, the G389R mutation in exon 13 of the MAPT gene was also detected in individuals with bvFTD or frontotemporal dementia with parkinsonism and presented with early-onset dementia and rapid progression (22). MAPT mutation carriers may have a prominent semantic impairment but this is presents only rarely, nor other forms of PPA. In contrast, GRN mutations can present as a PPA syndrome and bvFTD (1). Unlike the other two major genetic groups, C9orf72 repeat expansions can cause FTD-ALS, FTD or ALS alone (1,6–10). Similarly, frontotemporal dementia with parkinsonism can occur in affected individuals of a family with C9orf72 repeat expansions but is uncommon in China (6). To date, eight variants of the CHCHD10 gene were detected in Chinese frontotemporal degeneration individuals, including A21A, H22Y, P23L, P24L, A32D, V57E, P23S, and P89L. All variants were reported only in the Chinese population and located in CHCHD10 exon 2 except P89L. CHCHD10 mutations can cause SD, bvFTD, FTD-ALS and ALS alone (1,3,11,12). Two mutations (G97E and T127A) in the VCP gene were identified in Chinese families associated with Paget disease of bone and frontotemporal dementia (IBMPFD) and frontotemporal degeneration, respectively (13). Five variants (I334T, R444X, E653del, and L688Rfs‘14) in the TBK1 gene and six variants (c.174–2A>G, D40G, V128M, S229R, R302C and G419R) in the ANXA11 gene had been reported in Chinese individuals, which may be obligated to the ALS-FTD spectrum (1,14–17,19).

Much has been learned about genetic frontotemporal degeneration in the past decade, with the majority of autosomal dominant frontotemporal degeneration now accounting for a large proportion of that. However, most frontotemporal degeneration genetics studies have primarily focused on populations of European ancestry. There is much work to be done in improving the understanding of genetic profile associated with frontotemporal degeneration in China.

References

Conclusions

There are a small percentage of individuals who carry gene defects that contribute to the development of dementia. These genes can either cause, protect or increase the risk of developing dementia. Therefore having extensive knowledge of their family’s medical history becomes a crucial component to an individual seeking answers. This is especially true when they present with atypical, young-onset or rapidly progressive symptoms. If a potential link is established, a physician will order tests to look for brain accumulation of amyloid, tangles, alpha-synuclein, transactive response DNA binding protein 43 kD (TDP-43) and other pathogenic proteins to indicate the presence of dementia.

By delving deeper into potential causes, genetic testing offers a precise molecular diagnosis. If confirmed, healthcare professionals can provide information, guidance, and support in order to help make choices in their personal lives, related to their own personal risks, having children, and planning for the future.

As explored in the two essays from China, autosomal dominant Alzheimer's disease can be a particular burdensome form of the condition as it tends to affect people between the ages of 30 and 50. The hereditary component of this form of the disease merits further study across different ethnic cultures to assess the heterogeneity in the pathogenesis of Alzheimer's disease. Frontotemporal degeneration (FTD) is yet another classification of dementia that strikes individuals at a younger age, usually under 65, with genetic factors. Though recent studies have advanced the understanding of frontotemporal dementia, these have primarily focused on individuals of European lineage. This means there is still a long way to go in order to enhance the knowledge of genetic profile associated with frontotemporal degeneration in China.

It must be pointed out that having a risk factor is not necessarily an absolute determinant about whether one will develop the condition. The advances made in genetic testing over the past 30 years have simply added to the dementia diagnostic toolbox in estimating its likelihood and the probabilities at a given age.
Additional references


