Published in final edited form as:

Curr Neurol Neurosci Rep. 2012 October ; 12(5): 502–510. doi:10.1007/s11910-012-0296-1.

New Approaches to Genetic Counseling and Testing for Alzheimer's Disease and Frontotemporal Degeneration

Jill S. Goldman, M.S., M.Phil, CGC

Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, 630 W. 168th St., P & S Box 16, New York, NY 10032, (tel) 212-305-7382, (fax) 212-342-5144

Jill S. Goldman: jg2673@columbia.edu

Abstract

The discovery of new autosomal dominant and susceptibility genes for Alzheimer's disease and frontotemporal dementia is revealing important new information about the neurodegenerative process and the risk for acquiring these diseases. It is becoming increasingly clear that both the mechanisms that drive these diseases and their phenotypes overlap. New technologies will assist access to genetic testing but may increase difficulty with genetic test interpretation. Thus, the process of genetic counseling and testing for these diseases is becoming more complex. This paper will review current knowledge on the genetics of AD and FTD and suggest clinical guidelines for helping families to navigate through these complexities. The implications of future discoveries will be offered.

Keywords

Alzheimer's disease; Frontotemporal degeneration; Genetics; Genetic counseling; Genetic testing; Neurogenetics; Family history

Introduction

Genetic testing for the Alzheimer's disease (AD) and frontotemporal degeneration (FTD) is changing rapidly both because of new technology and the discovery of new genes. This article will discuss the present state of testing, acknowledging that guidelines will change as soon as the cost of genetic testing decreases with advancing technologies and/or new therapies are discovered. Because there are multiple genes for each disease and symptoms of AD and FTD often overlap, current genetic testing can be extensive and expensive. The future of genetic testing for dementia with next-generation sequencing may involve "dementia genetic testing panels" that examine regions of all pertinent genes. Even this technology has limitations and will miss certain mutations, particularly in those genes that have intronic or copy number variations. In this review, current criteria and protocols for clinical genetic testing and genetic research will be discussed, and suggestions will be offered about future directions.

Disclosure

No potential conflicts of interest relevant to this article were reported.

The Genetics of Alzheimer's Disease

Early-Onset Familial Alzheimer's Disease

AD is the most common dementia and up to 80% is believed to have some genetic etiology [1]. However, only 1–5% of the disease follows an autosomal dominant inheritance pattern [2, 3]. The presenilin 1 and 2 (*PSEN1*, *PSEN2*) and the amyloid precursor protein (*APP*) genes account for about 80% of these cases of early-onset familial AD (EOFAD) [4]. Any other autosomal genes remain undiscovered. Although most autosomal dominant cases have onset under the age of 65, late-onset cases are also found in these families [5].

Mutations in *PSEN1* on chromosome 14 account for at least 50% of EOFAD. Mutations in *APP* on chromosome 21 account for another 10–15%, and mutations in *PSEN2* on chromosome 1 are very rare except in families of Volga German origin [6, 7, 8, 9, 1]. In addition to single-base changes, duplications in *APP* and a deletion in *PSEN2* have been reported [11, 12]. Inter- and intra-familial phenotypic variations are common for all these genes, including age of onset (29–88) and symptomatology. Seizures are more common in these autosomal dominant cases and disease duration is usually shorter [11]. All 3 genes are highly penetrant, although several carriers of *PSEN2* mutations have lived into their 80s without symptoms and died of other causes [11].

In addition to mutations in these 3 genes, mutations in genes responsible for autosomal dominant frontotemporal degeneration (*MAPT*, *PGRN*, *C9ORF72*) and familial prion disease (*PRNP*), have been found in families that were clinically diagnosed with AD [13, 14, 15, 16, 17, 18, 19, 20, 21, 22]. When genetic testing of the autosomal dominant AD genes does not reveal a mutation, testing for *MAPT*, *PGRN*, *C9ORF72*, and *PRNP* should be considered.

Late-Onset Alzheimer's Disease

A much larger percentage of AD is due to risk factor or susceptibility genes. The apolipoprotein E gene (*APOE*) is associated with the greatest risk of developing the disease, accounting for 20–29% of late-onset AD risk [23, 24, 25]. *APOE* has 3 different allelic forms, $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, which lead to 6 possible genotypes, *APOE* $2\epsilon / \epsilon 2$, $2\epsilon / \epsilon 3$, $2\epsilon / \epsilon 4$, $3\epsilon / \epsilon 3$, $3\epsilon / \epsilon 4$, $4\epsilon / \epsilon 4$. Individuals with the *APOE* $3/4$ genotype have approximately a 2–3 fold lifetime risk of developing AD over the background risk which is about 10.4% [26], whereas those with *APOE* $4/4$ have up to a 15 fold risk [27]. Risk is higher in women than men [28]. Research indicates that *APOE* 4 lowers the age of onset and increases the rate of decline [29, 30, 31]. Approximately 41% of individuals with AD have an *APOE* $3/4$ as compared to about 21% of normal controls, and about 13% of AD cases have *APOE* $4/4$ compared to less than 1% of normal controls [32]. Additionally up to 50% of people with a single *APOE* 4 never develop AD [2]. Thus, although *APOE* 4 increases the risk of AD, it is neither sufficient nor necessary for developing AD. Many guidelines have been written concerning the use of *APOE* genetic testing. None of these encourage *APOE* genetic testing for either diagnostic or predictive testing [33, 34, 35, 36]. Importantly, with or without knowing *APOE* status, having a parent with AD confers a lifetime risk of about 2.5 times that of not having a parent with the disease [37, 26]. Having more relatives with AD may further increase the risk [38].

Genome-Wide Association Studies and Other Risk Genes

Genome-wide association studies (GWAS) have detected more than forty risk alleles for late-onset AD. All of these studies indicate that *APOE* confers substantially more risk than any other locus. Replicated results indicate that *PICALM* (the phosphatidylinositol binding clathrin assembly protein gene), *CLU* (the clusterin gene), and *CR1* (the complement

component [3b/4b] receptor 1 gene) are associated with increased AD risk in people of European ancestry [39, 40]. Other loci that have been replicated in studies include *SORL1*, *BIN1*, *EXOC3L2*, *GAB2*, *TNK1*, *LOC651924*, *GWA_14q32.13*, *PGBD1*, *GALP* [41, 42]. Although *PICALM*, *CLU*, and *BIN1* have also been found as susceptibility loci in African-Americans and Caribbean Hispanics, susceptibility genes may differ in different populations [43, 44].

To further elucidate late-onset risk, several GWAS studies are pursuing the endophenotypes of AD including age of onset and psychosis and specific cognitive profiles. It is clear that such features of AD are influenced by genetic and probably epigenetic factors [45, 46].

Although the identification of susceptibility (risk) loci is essential to the understanding of disease mechanisms and to drug development, the individual small effect on risk is of little clinical use for either assisting diagnosis or in prediction of disease [40, 47]. Additionally it is estimated that as many as 300 loci may eventually be implicated in AD risk as well as environmental or epigenetic factors.

Genetic Counseling and Testing for AD and other Dementias

Genetic testing for dementia is not straightforward. Not only are multiple genes involved, but the cost and the impact on family members must be considered. At the present time in the United States, CLIA certified testing of the 3 autosomal dominant genes that cause AD is only available through Athena Diagnostics. Both individual gene sequencing and a panel are available but remain very expensive. Often insurance will not cover diagnostic testing and will almost never cover predictive testing. Additionally, the impact on insurance should be discussed. The 2008 Genetic Information Nondiscrimination Act (GINA) protects against health insurance and employment discrimination, but not long-term care or life insurance [48]. Thus, asymptomatic individuals should consider getting long-term care and/or life insurance before they undergo testing. Testing strategies must be designed with family consultation.

Deciding whether genetic testing is appropriate can also be complicated, and should always include informed consent. The following issues should be considered:

- The clinical utility: will the test contribute to diagnosis and/or treatment?
- How likely is a genetic etiology?
- Does the patient have the capacity to consent?
- Who else in the family should be present (or consulted) for a discussion of possible genetic etiology and testing?
- What will be the effect of testing on other family members and do they want to know?
- Will insurance cover testing or can the family pay out of pocket?
- How will testing affect insurance coverage for asymptomatic individuals (GINA)?

Testing of an affected individual for AD autosomal dominant genes: (Figure 1)

Prior to considering genetic testing for one of the autosomal dominant genes, a detailed 3 generational family history should be taken. Without evidence of autosomal dominant inheritance, finding a mutation in *PSEN 1*, *PSEN 2*, *APP* is highly unlikely. However, a negative family history could be caused by: loss of contact with family, relatives dying at an

early age before they would have shown symptoms, or non-paternity. If the patient has early-onset AD (younger than 60 years of age) and the family wishes to know more about genetic risk, testing might still be appropriate.

Although a positive autosomal dominant genetic test confirms a diagnosis of AD in an affected individual, genetic testing is rarely performed for diagnostic purposes. Likewise, negative testing will not negate the clinical diagnosis. *APOE* testing will not confirm diagnosis or give significant information about a relative's risk. Also, genetic testing will not change treatment, although it may allow drug trial eligibility. Therefore, there are 2 main reasons for genetic testing of a patient with AD: 1. to inform the family of a genetic cause, 2. to become a candidate for a research study.

Diagnostic genetic testing should not be performed without genetic counseling for the patient and at least one family member. The presence of another family member is important since informed consent is required for genetic testing. Genetic information is confusing and may not be fully understood by someone diagnosed with dementia. The implications of a positive test should be discussed as well as how these results will be communicated to other family members. Patients and their families should understand that multiple possible results may be revealed: a definitive mutation in one of the genes, no mutation in any of the genes, a variant of unknown significance, or even mutations or variants in several genes. Literature review, functional studies, or specific modeling software may help predict whether a variant is benign, but the best evidence would come from seeing whether the variant segregates with the disease within the family. Such segregation studies are usually difficult because of prior deaths or family situations. Even a negative result does not entirely rule out an autosomal dominant cause since other genes may exist.

Predictive testing: (Figure 1)

Predictive testing for an autosomal dominant gene is a highly personal decision which demands extensive counseling. The majority of at-risk individuals do not initiate counseling and testing. Even those people who think they want testing often change their minds after counseling. Thus, those who elect to proceed generally cope well with the results [49]. It should be noted that in accordance with all existing guidelines, predictive testing should not be performed on children [50, 51].

Because of genetic heterogeneity, a mutation should be identified in the family before offering predictive testing. Only when there is a known family mutation will a negative result be informative. When there is a known mutation in the family, all guidelines suggest that the at-risk person seek counseling from a genetic testing center familiar with the multi-step, multidisciplinary predictive testing protocol recommended for Huntington disease [33]. This protocol usually requires several counseling sessions and baseline neurological and psychological evaluation prior to testing as well as in-person post-test counseling in the presence of a support person. Genetic counseling considers the benefits, risks, and limitations of testing, the effect on other family members and relationships, if and how to communicate results, and implications for insurance. As indicated above, most people are well-prepared for a positive result and cope sufficiently well.

Because of its low sensitivity and clinical utility, *APOE* testing is not recommended for predictive purposes [34, 52, 33]. However, media attention and the availability of direct-to-consumer (DTC) testing have caused an increase in demand for *APOE* testing. In carefully designed research settings, the Risk Evaluation and Education for Alzheimer's Disease Study (REVEAL) has demonstrated that there are few adverse emotional effects from learning one's *APOE* status [53, 54, 55]. In fact, these studies also demonstrated that people were motivated to find out their genetic status in order to plan for insurance and make

lifestyle changes. However, the major lifestyle change that occurred after learning *APOE* status was adding vitamins and dietary supplements. Without any medical advice or proven benefit, this behavior is questionable. Additionally, the acquisition of long-term care insurance was more common among those participants who learned that they were *APOE* $\epsilon 4$ positive [55]. However, this finding was part of a research study. Usually people are encouraged to buy insurance before not after genetic testing to avoid any discrimination. The acquisition of long-term care insurance is a practical application of this testing; however, if one has a family history of AD, the lack of an $\epsilon 4$ allele does not significantly change one's risk status and should not be used as a disincentive to purchasing long-term care insurance. In reality, testing *APOE* is neither wrong nor right. In certain situations a patient may be more motivated to alter lifestyle in order to lower modifiable risk factors such as those for cardiovascular (CV) risk [56]. Since CV risk factors are particularly precarious in *APOE* $\epsilon 4$, testing might give these patients the impetus they need to change their lifestyle [57]. Since CV risk factors such as hypertension, hypercholesterolemia, and diabetes are associated with increased AD risk, even *APOE* $\epsilon 4$ negative patients should be living a heart healthy lifestyle.

Clinicians should also be aware that *APOE* testing is available DTC and patients may confront their doctors with a laundry list of risk factors including *APOE*. Some patients may have little idea of what their results mean and will need interpretation from their physician.

Prenatal testing and preimplantation genetic diagnosis

Reproductive options are one of the most common reasons that people at risk for AD present to a genetic counselor. The parent-to-be may wish to ensure that the causal gene not be passed to offspring. In this situation, preimplantation genetic diagnosis (PGD) may be performed. Prenatal testing is not advised. Since pregnancy termination cannot be ensured, testing a fetus would be similar to testing a child. Before considering testing a fetus or pregnancy, a causal mutation must be confirmed in the family. Extensive genetic counseling is recommended before PGD. Issues to be discussed in these sessions include not only the specifics about the process, the genetics, and the disease, but whether the parents want to learn their own genetic status, the expected age of onset for the potentially affected parent, and whether that will affect the ability to parent, whether the unaffected parent will be able to care for the child and affected parent, and how the disease in the affected parent might impact the child [58, 59].

The Genetics of Frontotemporal Degeneration

Frontotemporal degeneration (previously known as frontotemporal dementia) is a group of neurodegenerative diseases that typically present with personality and behavioral changes (behavioral variant frontotemporal dementia, bv FTD) or language difficulty (primary progressive aphasia, PPA). Although FTD is among the most common presenile dementias, the range of onset is quite wide (30s–80s years of age). New criteria for bvFTD have recently been published and includes disinhibition, apathy, loss empathy, perseverative/compulsive behaviors, hyperorality, and executive dysfunction [60]. The FTD associated PPA syndromes include non-fluent progressive aphasia and semantic dementia [61, 62]. Corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are closely related diseases. Patients with FTD may also develop ALS and/or parkinsonism [63].

The understanding of the pathogenesis of FTD has changed dramatically over the last ten years, with the newest FTD gene being uncovered just a few months ago. Unlike AD, FTD is actually a group of diseases each with its unique pathology. Approximately 40% of FTD is a tauopathy, as is AD. However, whereas in AD equal amounts of 3R and 4R tau are abnormally hyperphosphorylated, in FTD the tau ratio is shifted to 3R tau in Pick's disease

or 4R tau in CBD and PSP. Mutations in the microtubule associated protein tau gene (*MAPT*) can cause any of the tau pathologies [64]. FTD with tau positive pathology is now referred to as FTLT-tau.

The most common FTD pathology, occurring in 50% of cases, is an accumulation of the TAR DNA binding protein 43 (TDP-43). Such cases are now referred to as FTLT-TDP-43. In addition to sporadic cases, this pathology is found in individuals with mutations in the progranulin gene (*PGRN*), the valosin-containing protein (*VCP*), the TDP-43 gene (*TARDP*), and the new *C9ORF72* gene. A third pathology found in about 10% of cases has an accumulation of the fused in sarcoma protein (FUS). This pathology is now FTLT-FUS. [64] Mutations in the FUS gene may be a very rare cause of FTD and have been reported as a cause of familial ALS [65]. Even with FTLT-FUS pathology, mutations in this gene are unlikely to be found [66, 67]. Finally there are very rare genetic forms of FTD with *CHMP2B* mutations which display tau negative, TDP-4 negative, FUS negative, ubiquitin positive pathology, FTLT-U [67].

Although a positive family history of neurological disease is found in up to 50% of FTD cases, only about 10–25% display an autosomal dominant pattern [68, 69, 70]. As seen above, FTD is genetically heterogeneous with at least 7 genes being associated with autosomal dominant cases. Of the autosomal dominant genes, *MAPT* and *PGRN* each account for about 7% of all cases and up to 25% of autosomal dominant cases depending on the study population (countries such as Sweden with founder mutations may have larger percentages of particular genetic cases). *PGRN* is also responsible for about 3% of sporadic FTD. Very recently the *C9ORF72* gene was identified as the gene responsible for about 12% of autosomal dominant cases and 3% of sporadic cases of FTD in which there was only a single case of the disease. A great majority of hereditary FTD/ALS cases are linked to this gene. Additionally this gene is responsible for 24–46% of familial ALS and 4–21% of sporadic ALS depending on the population [71, 72]. Unlike any of the other genes mentioned in this paper, the *C9ORF72* mutation leads to a huge expansion of a GGGGCC hexanucleotide in a non-coding part of this gene. The variations in phenotype and penetrance, of this mutation are still being determined. Additionally more studies will need to determine if anticipation occurs as it does with many other repeat diseases [71, 72, 77, 78].

Clinical testing for this gene is expected to be available in the near future, but at present, genetic testing is only available through research laboratories. *VCP* is a rare gene associated with FTD in conjunction with inclusion-body myopathy with Paget disease of bone. *CHMP2B*, *TARDP*, and *FUS* mutations are extremely rare.

A significant number of FTD cases have some family history but do not meet criteria for autosomal dominant inheritance. This is similar to the family clustering that is found in AD. The most likely explanation is the presence of susceptibility genes similar to APOE. Several FTD GWAS and association studies have uncovered potential susceptibility loci. However, since results have not been replicated, no conclusions can be drawn at this time [73, 74, 75].

Genetic testing for FTD

As with genetic testing for Alzheimer's disease, FTD genetic testing is expensive and complicated. For that reason, an algorithm was developed for sequential genetic testing [76]. Genetic testing for FTD is greatly facilitated by having a pathological diagnosis on an affected family member. An autopsy will guide genetic testing by eliminating the need to test certain genes (e.g. knowing that a relative had FTLT-TDP-43 would eliminate *MAPT*). However, autopsy information is not usually available. Thus, the sequence of genetic tests for symptomatic patients usually depends on the clinical symptoms and family history.

The first step in determining the order for genetic testing for FTD is to take a detailed family history. The *C9ORF72* gene is most consistent with an autosomal dominant family history of FTD and ALS. The most common presenting symptom is bvFTD. Psychosis as an early symptom appears to be more frequent with the *C9ORF72* expansion than with mutations in other genes. Additionally memory loss and anxiety are common. [77, 78] Studies about the clinical phenotype of *C9ORF72* mutation carriers are on-going [77, 78]. In At the time of this writing, CLIA testing is not yet available; hence, testing would need to occur through a research laboratory. Autosomal family histories without ALS are likely due to mutations in either *PGRN* or *MAPT*, with PNFA and impaired memory more commonly found with *PGRN*. Both inter-familial and intra-familial phenotypic variation is very common in all genetic forms, and there is phenotypic overlap between genes. (See [76, 80, 81] for complete discussion). As with AD, without a known or suspected family history of FTD, testing for autosomal dominant genes is less likely to yield a mutational finding. However, *PGRN* and *C9ORF72* mutations have been found in sporadic cases [71, 72, 79]. If the family is motivated to test and has the financial means, testing can proceed. Families should also be encouraged to consider autopsy for definitive diagnosis and guidance for any future genetic testing of brain tissue. Since autopsies can be quite expensive, families might wish to participate in research that might include autopsy.

Predictive genetic testing and PGD for FTD

As with AD, predictive testing for FTD should occur only after a causal mutation has been found in the family. Genetic testing should be preceded by genetic counseling in accordance with the Huntington Disease protocol which is described in the AD predictive testing section of this article. Preimplantation genetic diagnosis can be performed in light of a known mutation in one of the FTD genes.

Future directions for genetic testing of dementia

With the advent of next generation sequencing, concurrent genetic testing of many genes should be faster and less expensive. This technology will provide panels to test many dementia genes. With advancing technology comes greater complexity in the interpretation of genetic results. Although a genetic diagnosis may be quicker using this technique, it will vastly increase the number of variants of unknown significance, and, therefore, possible confusion for doctors and their patients. Patients will have to be informed about this possibility. Additionally, genetic counseling will have to entail a discussion of all the genes being tested. Each gene could potentially have differences in penetrance and expression and thus cannot be grouped together.

A second factor that will change future genetic testing will be drug discovery. Once interventions or even drug trials are available, the reason to pursue predictive testing of autosomal dominant genes will change, especially for people at-risk. However, for the vast majority of people whose overall risk will be dependent on multiple genetic, epigenetic, and environmental factors, we are still a long way from determining who will develop AD or FTD. A future genetic risk panel may determine overall risk but not whether the person is developing the disease. Other biomarkers such as cerebrospinal fluid Amyloid Tau levels, will be more suitable to determine progression to disease.

Conclusions

At present, the majority of autosomal dominant genes responsible for familial AD and FTD have been uncovered. As seen from current GWAS studies, many other genes will be found that contribute to the overall risk of developing these diseases. Additionally epigenetic and environmental factors are yet to be revealed. Thus, much remains unknown about how these

additional factors influence the variations in phenotypes seen even within autosomal dominant families. Genetic testing of the autosomal dominant genes can predict whether one will develop AD or FTD, but not when or how symptoms will present. In fact, as seen in recent studies, AD and FTD phenotypes can overlap. Navigating the complexities of AD and FTD genetics demands a thorough understanding of not only the genes being tested but the implications of testing on the patient and the family. As technologies change, genetic testing will become more accessible but harder to interpret. Thus, genetic counseling, which is essential now before and after testing, will become even more so in the future.

References

1. Gatz M, Reynolds CA, Fratiglioni L, et al. Role of genes and environments for explaining Alzheimer disease. *Arch Gen Psychiatry*. 2006; 63:168–174. [PubMed: 16461860]
2. Bekris LM, Yu CE, Bird TD, Tsuang DW. Genetics of Alzheimer disease. *J Geriatr Psychiatry Neurol*. 2010; 23:213–227. [PubMed: 21045163]
3. Roses AD. On the metabolism of apolipoprotein E and the Alzheimer diseases. *Exp Neurol*. 1995; 132:149–156. [PubMed: 7789455]
4. Raux G, Guyant-Marechal L, Martin C, et al. Molecular diagnosis of autosomal dominant early onset Alzheimer's disease: an update. *J Med Genet*. 2005; 42:793–795. [PubMed: 16033913]
5. Brickell KL, Steinbart EJ, Rumbaugh M, et al. Early-onset Alzheimer disease in families with late-onset Alzheimer disease: a potential important subtype of familial Alzheimer disease. *Arch Neurol*. 2006; 63:1307–1311. [PubMed: 16966510]
6. Sherrington R, Froelich S, Sorbi S, et al. Alzheimer's disease associated with mutations in presenilin 2 is rare and variably penetrant. *Hum Mol Genet*. 1996; 5:985–988. [PubMed: 8817335]
7. Levy-Lahad E, Wijsman EM, Nemens E, et al. A familial Alzheimer's disease locus on chromosome 1. *Science*. 1995; 269:970–973. [PubMed: 7638621]
8. Rogaev EI, Sherrington R, Rogaeva EA, et al. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. *Nature*. 1995; 376:775–778. [PubMed: 7651536]
9. Goate A, Chartier-Harlin MC, Mullan M, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature*. 1991; 349:704–706. [PubMed: 1671712]
10. Levy-Lahad E, Tsuang D, Bird TD. Recent advances in the genetics of Alzheimer's disease. *J Geriatr Psychiatry Neurol*. 1998; 11:42–54. [PubMed: 9877525]
11. Jayadev S, Leverenz JB, Steinbart E, et al. Alzheimer's disease phenotypes and genotypes associated with mutations in presenilin 2. *Brain*. 2010; 133:1143–1154. [PubMed: 20375137]
12. Rovelet-Lecrux A, Hannequin D, Raux G, et al. APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. *Nat Genet*. 2006; 38:24–26. [PubMed: 16369530]
13. Reed LA, Grabowski TJ, Schmidt ML, et al. Autosomal dominant dementia with widespread neurofibrillary tangles. *Ann Neurol*. 1997; 42:564–572. [PubMed: 9382467]
14. van Swieten JC, Stevens M, Rosso SM, et al. Phenotypic variation in hereditary frontotemporal dementia with tau mutations. *Ann Neurol*. 1999; 46:617–626. [PubMed: 10514099]
15. Rademakers R, Dermaut B, Peeters K, et al. Tau (MAPT) mutation Arg406Trp presenting clinically with Alzheimer disease does not share a common founder in Western Europe. *Hum Mutat*. 2003; 22:409–411. [PubMed: 14517953]
16. Momeni P, Pittman A, Lashley T, et al. Clinical and pathological features of an Alzheimer's disease patient with the MAPT Delta K280 mutation. *Neurobiol Aging*. 2009; 30:388–393. [PubMed: 17723255]
17. Baker M, Mackenzie IR, Pickering-Brown SM, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature*. 2006; 442:916–919. [PubMed: 16862116]

18. Brouwers N, Nuytemans K, van der Zee J, et al. Alzheimer and Parkinson diagnoses in progranulin null mutation carriers in an extended founder family. *Arch Neurol*. 2007; 64:1436–1446. [PubMed: 17923627]
19. Brouwers N, Sleegers K, Van Broeckhoven C. Molecular genetics of Alzheimer's disease: an update. *Ann Med*. 2008; 40:562–583. [PubMed: 18608129]
20. Kumar N, Boeve BF, Boot BP, et al. Clinical characterization of a kindred with a novel 12-octapeptide repeat insertion in the prion protein gene. *Arch Neurol*. 2011; 68:1165–1170. Case study demonstrating overlapping features of AD and prion disease and importance of considering genetic testing of prion disease with an autosomal dominant family history of dementia. [PubMed: 21911696]
21. Jayadev S, Nochlin D, Poorkaj P, et al. Familial prion disease with Alzheimer disease-like tau pathology and clinical phenotype. *Ann Neurol*. 2011; 69:712–720. [PubMed: 21416485]
22. Majounie E, Abramzon Y, Renton AE, et al. Repeat expansion in C9ORF72 in Alzheimer's disease. *N Engl J Med*. 2012; 366:283–284. [PubMed: 22216764]
23. Meyer MR, Tschanz JT, Norton MC, et al. APOE genotype predicts when--not whether--one is predisposed to develop Alzheimer disease. *Nat Genet*. 1998; 19:321–322. [PubMed: 9697689]
24. Slioter AJ, Cruts M, Kalmijn S, et al. Risk estimates of dementia by apolipoprotein E genotypes from a population-based incidence study: the Rotterdam Study. *Arch Neurol*. 1998; 55:964–968. [PubMed: 9678314]
25. Seshadri S, Drachman DA, Lippa CF. Apolipoprotein E epsilon 4 allele and the lifetime risk of Alzheimer's disease. What physicians know, and what they should know. *Arch Neurol*. 1995; 52:1074–1079. [PubMed: 7487559]
26. Cupples LA, Farrer LA, Sadovnick AD, Relkin N, Whitehouse P, Green RC. Estimating risk curves for first-degree relatives of patients with Alzheimer's disease: the REVEAL study. *Genet Med*. 2004; 6:192–196. [PubMed: 15266206]
27. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993; 261:921–923. [PubMed: 8346443]
28. Payami H, Montee K, Grimslid H, Shattuc S, Kaye J. Increased risk of familial late-onset Alzheimer's disease in women. *Neurology*. 1996; 46:126–129. [PubMed: 8559360]
29. Khachaturian AS, Corcoran CD, Mayer LS, Zandi PP, Breitner JC. Apolipoprotein E epsilon4 count affects age at onset of Alzheimer disease, but not lifetime susceptibility: The Cache County Study. *Arch Gen Psychiatry*. 2004; 61:518–524. [PubMed: 15123497]
30. Blacker D, Haines JL, Rodes L, et al. ApoE-4 and age at onset of Alzheimer's disease: the NIMH genetics initiative. *Neurology*. 1997; 48:139–147. [PubMed: 9008509]
31. Martins CA, Oulhaj A, de Jager CA, Williams JH. APOE alleles predict the rate of cognitive decline in Alzheimer disease: a nonlinear model. *Neurology*. 2005; 65:1888–1893. [PubMed: 16380608]
32. Jarvik G, Larson EB, Goddard K, Schellenberg GD, Wijsman EM. Influence of apolipoprotein E genotype on the transmission of Alzheimer disease in a community-based sample. *Am J Hum Genet*. 1996; 58:191–200. [PubMed: 8554056]
33. Goldman JS, Hahn SE, Catania JW, et al. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med*. 2011; 13:597–605. Newest guidelines on genetic counseling and testing for Alzheimer's disease. [PubMed: 21577118]
34. AGS Ethics Committee. Genetic testing for late-onset Alzheimer's disease. *J Am Geriatr Soc*. 2001; 49:225–226. [PubMed: 11207878]
35. Statement on use of apolipoprotein E testing for Alzheimer disease. American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer disease. *JAMA*. 1995; 274:1627–1629. [PubMed: 7474250]
36. Post SG, Whitehouse PJ, Binstock RH, et al. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *JAMA*. 1997; 277:832–836. [PubMed: 9052715]
37. Silverman JM, Raiford K, Edland S, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part VI. Family history assessment: a multicenter study of first-degree relatives

- of Alzheimer's disease probands and nondemented spouse controls. *Neurology*. 1994; 44:1253–1259. [PubMed: 8035925]
38. Jayadev S, Steinbart EJ, Chi YY, Kukull WA, Schellenberg GD, Bird TD. Conjugal Alzheimer disease: risk in children when both parents have Alzheimer disease. *Arch Neurol*. 2008; 65:373–378. [PubMed: 18332250]
 - 39•. Jun G, Naj AC, Beecham GW, et al. Meta-analysis confirms CR1, CLU, and PICALM as Alzheimer disease risk loci and reveals interactions with APOE genotypes. *Arch Neurol*. 2011; 67:1473–1484. A multicenter database analysis of case control studies demonstrating association of loci with AD risk. [PubMed: 20697030]
 40. Seshadri S, Fitzpatrick AL, Ikram MA, et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA*. 2010; 303:1832–1840. [PubMed: 20460622]
 41. Belbin O, Carrasquillo MM, Crump M, et al. Investigation of 15 of the top candidate genes for late-onset Alzheimer's disease. *Hum Genet*. 2011; 129:273–282. [PubMed: 21132329]
 - 42•. Reitz C, Cheng R, Rogaeva E, et al. Meta-analysis of the association between variants in SORL1 and Alzheimer disease. *Arch Neurol*. 2011; 68:99–106. Large replication meta-analysis confirming association between SORL1 and AD risk. [PubMed: 21220680]
 - 43•. Logue MW, Schu M, Vardarajan BN, et al. A comprehensive genetic association study of Alzheimer disease in African Americans. *Arch Neurol*. 2011; 68:1569–1579. One of a very few studies on AD risk in African-Americans indicating that some risk factors may be the same as for Caucasians, but there may be other factors as well. [PubMed: 22159054]
 44. Lee JH, Cheng R, Barral S, et al. Identification of novel loci for Alzheimer disease and replication of CLU, PICALM, and BIN1 in Caribbean Hispanic individuals. *Arch Neurol*. 2011; 68:320–328. [PubMed: 21059989]
 45. Kamboh MI, Barmada MM, Demirci FY, et al. Genome-wide association analysis of age-at-onset in Alzheimer's disease. *Mol Psychiatry*. 2011
 46. Hollingworth P, Sweet R, Sims R, et al. Genome-wide association study of Alzheimer's disease with psychotic symptoms. *Mol Psychiatry*. 2011
 47. Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. *Nat Rev Neurol*. 2011; 7:137–152. [PubMed: 21304480]
 48. Hudson KL, Holohan MK, Collins FS. Keeping pace with the times--the Genetic Information Nondiscrimination Act of 2008. *N Engl J Med*. 2008; 358:2661–2663. [PubMed: 18565857]
 49. Steinbart EJ, Smith CO, Poorkaj P, Bird TD. Impact of DNA testing for early-onset familial Alzheimer disease and frontotemporal dementia. *Arch Neurol*. 2001; 58:1828–1831. [PubMed: 11708991]
 50. Ethical issues with genetic testing in pediatrics. *Pediatrics*. 2001; 107:1451–1455. [PubMed: 11389275]
 51. American Society of Human Genetics Board of Directors, American College of Medical Genetics Board of Directors. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. *Am J Hum Genet*. 1995; 57:1233–1241. [PubMed: 7485175]
 52. Relkin NR, Kwon YJ, Tsai J, Gandy S. The National Institute on Aging/Alzheimer's Association recommendations on the application of apolipoprotein E genotyping to Alzheimer's disease. *Ann N Y Acad Sci*. 1996; 802:149–176. [PubMed: 8993494]
 53. Gooding HC, Linnenbringer EL, Burack J, Roberts JS, Green RC, Biesecker BB. Genetic susceptibility testing for Alzheimer disease: motivation to obtain information and control as precursors to coping with increased risk. *Patient Educ Couns*. 2006; 64:259–267. [PubMed: 16860524]
 54. Cassidy MR, Roberts JS, Bird TD, et al. Comparing test-specific distress of susceptibility versus deterministic genetic testing for Alzheimer's disease. *Alzheimers Dement*. 2008; 4:406–413. [PubMed: 19012865]
 - 55•. Roberts J, Christensen K, Green R. Using Alzheimer's disease as a model for genetic risk disclosure: implications for personal genomics. *Clin Genet*. 2011; 80:407–414. Latest REVEAL study discussion of releasing APOE information to patients. [PubMed: 21696382]
 56. Schipper HM. Presymptomatic apolipoprotein E genotyping for Alzheimer's disease risk assessment and prevention. *Alzheimers Dement*. 2011; 7:e118–123. [PubMed: 21665554]

57. Caselli RJ, Dueck AC, Locke DE, et al. Cerebrovascular risk factors and preclinical memory decline in healthy APOE epsilon4 homozygotes. *Neurology*. 2011; 76:1078–1084. [PubMed: 21325652]
58. Towner D, Loewy RS. Ethics of preimplantation diagnosis for a woman destined to develop early-onset Alzheimer disease. *JAMA*. 2002; 287:1038–1040. [PubMed: 11866654]
59. Verlinsky Y, Rechitsky S, Verlinsky O, Masciangelo C, Lederer K, Kuliev A. Preimplantation diagnosis for early-onset Alzheimer disease caused by V717L mutation. *JAMA*. 2002; 287:1018–1021. [PubMed: 11866650]
- 60•. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011; 134:2456–2477. Newest clinical guidelines on criteria for FTD. [PubMed: 21810890]
61. Kertesz A. The overlapping syndromes of the pick complex. *Curr Alzheimer Res*. 2011; 8:224–228. [PubMed: 21524271]
62. Grossman M. Primary progressive aphasia: clinicopathological correlations. *Nat Rev Neurol*. 2010; 6:88–97. [PubMed: 20139998]
63. Espay AJ, Litvan I. Parkinsonism and frontotemporal dementia: the clinical overlap. *J Mol Neurosci*. 2011; 45:343–349. [PubMed: 21892619]
64. Cairns NJ, Bigio EH, Mackenzie IR, et al. Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. *Acta Neuropathol*. 2007; 114:5–22. [PubMed: 17579875]
65. Huey ED, Ferrari R, Moreno JH, et al. FUS and TDP43 genetic variability in FTD and CBS. *Neurobiol Aging*. 2011
- 66•. Snowden JS, Hu Q, Rollinson S, et al. The most common type of FTL-D-FUS (aFTLD-U) is associated with a distinct clinical form of frontotemporal dementia but is not related to mutations in the FUS gene. *Acta Neuropathol*. 2011; 122:99–110. A description of the clinical phenotype of FTL-D-FUS. [PubMed: 21424531]
- 67•. Josephs KA, Hodges JR, Snowden JS, et al. Neuropathological background of phenotypical variability in frontotemporal dementia. *Acta Neuropathol*. 2011; 122:137–153. An overview of clinicopathological phenotypes in FTD. [PubMed: 21614463]
68. Rohrer JD, Guerreiro R, Vandrovicova J, et al. The heritability and genetics of frontotemporal lobar degeneration. *Neurology*. 2009; 73:1451–1456. [PubMed: 19884572]
69. Seelaar H, Kamphorst W, Rosso SM, et al. Distinct genetic forms of frontotemporal dementia. *Neurology*. 2008; 71:1220–1226. [PubMed: 18703462]
70. Goldman JS, Farmer JM, Wood EM, et al. Comparison of family histories in FTL-D subtypes and related tauopathies. *Neurology*. 2005; 65:1817–1819. [PubMed: 16344531]
- 71•. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron*. 2011; 72:245–256. Discovery of the C9ORF72 gene. [PubMed: 21944778]
- 72•. Renton AE, Majounie E, Waite A, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron*. 2011; 72:257–268. Discovery of the C9ORF72 gene. [PubMed: 21944779]
73. Rollinson S, Rohrer JD, van der Zee J, et al. No association of PGRN 3'UTR rs5848 in frontotemporal lobar degeneration. *Neurobiol Aging*. 32:754–755. [PubMed: 19446372]
74. Vass R, Ashbridge E, Geser F, et al. Risk genotypes at TMEM106B are associated with cognitive impairment in amyotrophic lateral sclerosis. *Acta Neuropathol*. 2011; 121:373–380. [PubMed: 21104415]
75. Eriksen JL, Mackenzie IR. Progranulin: normal function and role in neurodegeneration. *J Neurochem*. 2008; 104:287–297. [PubMed: 17953663]
- 76•. Goldman JS, Rademakers R, Huey ED, et al. An algorithm for genetic testing of frontotemporal lobar degeneration. *Neurology*. 2011; 76:475–483. Description of an algorithm to navigate genetic testing for FTD. [PubMed: 21282594]
- 77•. Snowden JS, Rollinson S, Thompson JC, et al. Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations. *Brain*. 2012; 135:693–708.

Newest information on the clinical phenotype associated with the C9ORF72 gene mutation. [PubMed: 22300873]

- 78•. Mahoney CJ, Beck J, Rohrer JD, et al. Frontotemporal dementia with the C9ORF72 hexanucleotide repeat expansion: clinical, neuroanatomical and neuropathological features. *Brain*. 2012; 135:736–750. Newest information on the clinical phenotype associated with the C9ORF72 gene mutation. [PubMed: 22366791]
79. Le Ber I, van der Zee J, Hannequin D, et al. Progranulin null mutations in both sporadic and familial frontotemporal dementia. *Hum Mutat*. 2007; 28:846–855. [PubMed: 17436289]
80. Seelaar H, Rohrer JD, Pijnenburg YA, et al. Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review. *J Neurol Neurosurg Psychiatry*. 2011; 82:476–486. [PubMed: 20971753]
81. Rohrer JD, Warren JD. Phenotypic signatures of genetic frontotemporal dementia. *Curr Opin Neurol*. 2011; 24:542–549. [PubMed: 21986680]

Figure 1.

Protocol for exploratory genetic testing for autosomal dominant AD and predictive genetic testing: the sequence of steps for a symptomatic patient considering genetic testing for autosomal dominant dementia followed by predictive counseling after the identification of a mutation in a family member.

Table 1
Autosomal dominant genes associated with Alzheimer's disease and Frontotemporal degeneration

Gene	Disease	Inheritance	Range of onset (AAO)	Phenotypic features	Other phenotypic features	% of total FTD	% of autosomal dominant
PSEN1	AD	Autosomal dominant	25 –65 (42)	Global cognitive impairment	spastic paraparesis, seizures	<1%	50%
PSEN2	AD	Autosomal dominant	39 –88 (54)	Global cognitive impairment	Seizures	Very rare	Very rare
APP	AD	Autosomal dominant	(40–55) (51)	Global cognitive impairment	cerebral hemorrhages	<1%	10–15%
MAPT	FTD, CBD, PSP	Autosomal dominant	30s–70s (55)	bvFTD, PPA, CBD, PSP	Parkinsonism	1–7%	25%
PGRN	FTD	Autosomal dominant/Sporadic	35–89 (60)	bvFTD, PNFA, CBS	Psychosis, Episodic memory impairment parkinsonism	1–7%	25%
C9ORF72	FTD ALS	Autosomal dominant/Sporadic	34–74 (54)	PNFA, bvFTD, ALS	FTD/ALS alone or in combination	~12%	25%
CHMP2B	FTD	Autosomal dominant	46–65	bvFTD	Parkinsonism, dystonia, myoclonus, (ALS)	Very rare	Rare
VCP	FTD IBMPFD	Autosomal dominant	40–60	bvFTD	inclusion body myopathy Paget's disease of the bone, ALS	Very rare	Rare
TARDBP	ALS FTD?	Autosomal dominant	20–75	ALS	dementia	Very rare	Very rare
FUS	ALS FTD?	Autosomal dominant	20–66	ALS	dementia	Very rare	Very rare

References: [1,2, 4,11, 12,19,71,72, 79, 80, 81, 82,83]