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Alzheimer's Disease and Frontotemporal Dementia: The Current State of Genetics and Genetic Testing Since the Advent of Next-Generation Sequencing

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Abstract

The advent of next generation sequencing has changed genetic diagnostics allowing clinicians to test concurrently for phenotypically overlapping conditions such as Alzheimer's disease and frontotemporal dementia. However, to interpret genetic results, clinicians require an understanding of the benefits and limitations of different genetic technologies, such as the inability to detect large repeat expansions in such diseases as *C9orf72*-associated frontotemporal dementia and amyotrophic lateral sclerosis. Other types of mutations such as large deletions or duplications and triple repeat expansions may also go undetected. Additionally, the concurrent testing of multiple genes or the whole exome increases the likelihood of discovering variants of unknown significance. Our goal here is to review the current knowledge about the genetics of Alzheimer's disease and frontotemporal dementia and to suggest up-to-date guidelines for genetic testing for these dementias. Despite the improvements in diagnosis due to biomarker testing, Alzheimer's disease and frontotemporal dementia can have overlapping symptoms. When used appropriately, genetic testing can elucidate the diagnosis, specific etiology of the disease, provide information for the family, and eligibility for clinical trials. Prior to ordering genetic testing, clinicians must determine the appropriate genes to test, the types of mutations that occur in these genes, and the best type of genetic test to use. Without this analysis, interpretation of genetic results will be difficult. Patients should be counseled about the benefits and limitations of different types of genetic tests, so they can make an informed decision about testing.

1. Introduction

Advances in genetic technology have greatly reduced the cost of genetic testing and enabled rapid massively parallel analysis of genes, and as a result, produced significant

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developments in diagnostics and therapeutics. However, the efficacious use of this “next generation sequencing” (NGS) requires awareness of its limitations. Here we focus on how NGS technology has changed genetic testing for Alzheimer’s disease (AD) and frontotemporal dementia (FTD, also known as frontotemporal degeneration), two dementias that can overlap clinically. The goal of this paper is to provide physicians and genetic counselors updated guidelines for how and when to order genetic testing for AD and FTD. A PubMed literature search was used to review the most current information about Alzheimer’s disease and frontotemporal dementia genetics. We used this information to develop an algorithm for best practices for genetic testing of these diseases.

2.1 Alzheimer’s Disease

Approximately 1% of all AD is caused by mutations in autosomal dominant genes [1, 2]. A significantly larger number of cases demonstrate family clustering with both early and late-onset AD in the same family. In that the heritability of AD is between 60–80% [2, 3], many of the genetic mechanisms behind AD have yet to be elucidated.

2.1.1 Autosomal Dominant AD:

The genetics of autosomal dominant AD is well-described with three predominant genes identified. Presenilin 1 (*PSEN1*) accounts for about 80% of autosomal dominant cases. Presenilin 2 (*PSEN2*) is quite rare, except in families of Volga German ancestry, accounting for only 5% of cases. About 15% of autosomal dominant cases are due to mutations in the amyloid precursor protein gene (*APP*) [3]. More than 200 mutations have been described in *PSEN1*, with the majority being missense mutations, but also small duplications and deletions and larger deletions. The median age of onset in *PSEN1* mutation carriers is 43, with the great majority starting before the age of 60 [4]. Approximately 16 mutations have been reported in *PSEN2* according to the AD and FTD Mutation Database <http://www.molgen.ua.ac.be/admutations/> [5]. Onset is variable, usually between the ages of 40 and 70. *PSEN2* mutations have incomplete penetrance [6]. More than 50 different mutations (including small deletions and as well as duplications) have been reported in *APP*, with an age of onset between 45–60 years [6]. Whereas missense mutations in *APP* are fully penetrant, duplications show incomplete penetrance [6]. The phenotype conferred by these autosomal dominant mutations include the classic amnesic presentation, frontal variant AD with behavioral changes resembling FTD, logopenic primary progressive aphasia (PPA), spastic paraparesis, myoclonus, seizures, and parkinsonism [6, 7].

2.1.2 Non-autosomal dominant AD:

Sporadic AD also has a strong genetic component. The apolipoprotein E gene (*APOE*) is associated with a significant risk of both EOAD and LOAD. Of the 3 common *APOE* alleles ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$), $\epsilon 4$ is associated with a dose-dependent increased risk of AD. In Caucasians, the relative risk for $\epsilon 4$ heterozygotes is 3-fold and for homozygotes, about 15-fold [6]. Dose-dependent lowering of the age of onset is also associated with $\epsilon 4$ [8].

Relative risk differs across ethnicities [8]. $\epsilon 4$ is also associated with an increased risk of cardiovascular disease [9]. In contrast, $\epsilon 2$ confers a small degree of protection against AD

[6]. Because *APOE* is neither necessary or sufficient to cause AD, genetic testing of *APOE* is not recommended [10].

APOE $\epsilon 4$ -associated risk accounts for 20–70% of the overall non-Mendelian AD risk [8]. Genome-wide association studies (GWAS) and whole-exome sequencing (WES) studies have uncovered additional moderate risk genes. An autosomal dominant mutation in *ABCA7* was found in a Belgian late-onset family [11], but *ABCA7* variants have also been associated with an increased risk in African-Americans that equals the risk of *APOE* [12]. Risk variants in *SORL1* were found in both EOAD [13] and LOAD [6]. *TREM2* variants may increase risk of AD significantly [14, 15].

2.1.3 Small-effect genes

GWAS and WES also have identified many loci associated with LOAD risk, with wide replication for at least 20 loci. These include genes involved in the neural-immune system (e.g. *CLU*, *CR1*, *ABCA7*, *TREM2*), synaptic function (e.g. *PICALM* and *NIN1*), endocytosis (*PICALM*, *BIN1*, *SORL1*), and lipid metabolism (*APOE*, *CLU*, *ABCA7*) [3]. With the majority of LOAD risk odds ratios being between 1.1 to 1.3, there is currently little clinical value for a multigene prediction score, outside of selection of clinical trial participants [16]. Additionally, several rare variants in *APP* (p.Ala673Thr, rs63750847) and others in *PSEN1* would need to be factored in assessing overall risk [6, 17]. Other types of genetic variations may also contribute to LOAD risk including polymorphisms in the promoters of *PSEN1* [18–20], copy number variants (CNVs) [21], and variants in non-coding areas of the genome [6]. While genetic risk variants are very important for research, at the present time, individuals with LOAD should be counseled that, in all probability, genetic testing has no clinical significance.

2.2 Frontotemporal dementia

FTD accounts for approximately 10% of all dementias [22]. Unlike the universality of AD pathology with its amyloid plaques and hyperphosphorylated tau tangles, FTD has three underlying pathologies: approximately 40% has tau pathology, approximately 50% has TDP-43 pathology, and about 10% has FUS pathology [23]. FTD has two main symptom presentations: behavioral variant FTD (bvFTD), manifesting as behavioral and personality change, and primary progressive aphasia (PPA), which is further subdivided as non-fluent aphasia (nfPPA), semantic variant (svFTD), and logopenic PPA (usually with underlying AD pathology) [24, 25].

2.2.1 FTD Genetics

FTD is highly heritable with 30–50% of cases having a family history of FTD or related disease, of which 10–20% is autosomal dominant [3]. Three major genes contribute to the autosomal dominant cases: *MAPT*, *GRN*, and *C9orf72* and mutations are listed in the AD and FTD mutation database (<http://www.molgen.vib-ua.be/FTDMutations>) [5, 26]. Pathogenic and risk variants have been reported at much lower frequencies in several additional genes including *TARDBP* [27], *VCP* [28], *CHMP2B* [29], *ITM2B* [30], *TBP* [30], *DCTN1* [31], *SQSTM1* [32], *TREM2* [33], *UBQLN2* [34], *CHCHD10* [35], and *TBK1* [36].

[26]. The cumulative frequency of these genes accounts for less than 5% of all FTD [30]. However, founder effects may increase the prevalence of individual genes in certain populations (in Belgium *TBK1* has been reported as third most common FTD risk gene) [36].

MAPT was the first gene associated with FTD, originally known as frontotemporal dementia with parkinsonism linked to chromosome 17 or FTDP-17 [37]. *MAPT* accounts for 10–20% of autosomal dominant cases depending on the population and to date, more than 40 different pathogenic variants, mostly in exons 1 and 9–13, have been reported in this gene according to the AD and FTD Mutation Database (<http://www.molgen.vib-ua.be/FTDMutations>) [5]. One rare low penetrance variant in exon 7, p.A152T, has been shown to increase the risk for both FTD and AD and other neurodegenerative diseases [38, 39]. Very few sporadic cases have been reported [40]. The average age of onset for *MAPT* mutation carriers is 45–65 years [30, 41]. Penetrance is age-dependent approaching 100% after age 65. The *MAPT* phenotype is highly variable, even within families. bvFTD with disinhibition is the most common phenotype, but atypical parkinsonism including corticobasal syndrome (CBS), progressive supranuclear palsy (PSP), memory loss, and PPA have been reported [40]. Motor neuron disease (MND) is not a feature of *MAPT*-related FTD. Imaging usually reveals symmetrical frontotemporal atrophy and hypometabolism [30]. Tau pathology is found in all cases with a *MAPT* mutation.

GRN, also on chromosome 17 [42, 43], has at least 80 reported mutations. *GRN* accounts for about a quarter of autosomal dominant FTD and up to 5% of apparent sporadic cases [3]. *GRN* appears to be nearly 100% penetrant by age 80. Age of onset is typically somewhat older than that of *MAPT*, ranging from 35–89 [30]. Clinical phenotypes show significant inter- and intra-familial variability. bvFTD with apathy rather than disinhibition [43] is the most common presentation, but nPPA and CBS are not infrequent [30]. Early memory loss and hallucinations can be present. MND is not a part of this syndrome. *GRN* mutation carriers have more autoimmune disease than non-carriers [44, 45]. Imaging of *GRN* mutation carriers typically shows asymmetric atrophy involving the frontal, temporal, and parietal lobes [30]. *GRN* mutation carriers invariably have TDP-43 pathology on brain autopsy [46].

Mutations in *C9orf72* are due to intronic expansions of a hexanucleotide (GGGGCC) repeat. Not only are *C9orf72* expansions responsible for about 30% of familial FTD, but also up to 50% of familial amyotrophic lateral sclerosis (ALS), and about 88% of cases with symptoms of both FTD and ALS [47]. *C9orf72* expansions account for about 6% of apparent sporadic FTD [48]. *C9orf72*-associated FTD phenotypes are extremely variable. The most common presentations are bvFTD, ALS and FTD /ALS. parkinsonism, ataxia, chorea, and psychosis with hallucinations and delusions. Psychosis can occur any time during the disease, even as a prodromal symptom [49], and has been reported in 28–56% of cases [50]. *C9orf72* is thought to be less than 100% penetrant, but approximately 50% of carriers are affected by age 58 [48, 51] and 90% by age 70 [30]. PPA is a rarer presentation than with *GRN* or *MAPT* [50]. Like *GRN*, *C9orf72* is associated with an increased risk of autoimmune disease [45]. Imaging for *C9orf72* is more variable, but usually symmetrical and cerebellar atrophy can be a feature [52].

C9orf72 presents many unknowns. The repeat expansion is highly unstable with repeat numbers ranging from approximately 30 to thousands. The pathogenicity of 20–30 repeats is questionable [53]. Whether phenotype or age of onset correlates with repeat number is debatable, with most studies reporting no correlation [54, 55], although one study showed correlation with disease duration [51]. Hypermethylation may influence repeat length correlation [36]. However, the number of repeats can undergo somatic expansion with the number found in blood differing from that in the brain [50]. The cerebellar repeat number may be the best indication of age of onset [56]. Ambiguity about anticipation also exists [48, 57].

2.2.2 Genetic modifiers

GWAS and NGS studies have identified several genetic modifiers of FTD. The most significant genetic risk factor for TDP-43 pathology is *TMEM106B*, which was identified in a GWAS of FTLTDP pathology-confirmed cases and *GRN* mutation carriers [58]. The minor allele of *TMEM106B* risk SNPs may be protective in *GRN* mutation carriers, suggesting genotyping for these SNPs may be important clinically in helping to predict penetrance. *TMEM106B* SNPs also appear to modify *C9orf72* phenotype and cause later onset of dementia phenotypes [59]. The mechanism by which *TMEM106B* variants modulate risk of TDP-43 pathology is unknown, but multiple lines of evidence suggests effects on lysosomal function [59].

A polymorphism in *GRN* was associated with risk of AD and Parkinson's disease but not FTD [60]. A polymorphism in *MAPT* was associated with risk of FTD, AD, and Lewy body dementia [38, 39, 61]. Additionally, a homozygous mutation in *GRN* has been found to cause adult ceroid lipofuscinosis, a lysosomal storage disease [62]. The pathogenic role of *C9orf72* has been questioned since expansions have been found in 0.6% of controls. Some researchers hypothesize the need for a second hit in another gene before causing disease. In fact, *C9orf72* expansions have been found in conjunction with mutations in other genes such as *GRN* [48] and *TBK1* [63], and *SQSTM1* [64]. The fact that *C9orf72* and the great majority of the rarer FTD genes (other than *CHMP2B*) have been implicated in both ALS and FTD indicates that the two diseases are genetically and pathologically related.

2.3 Genetic and genomic technology in the study of AD and FTD

Technological advances in molecular biology have changed the field of molecular diagnosis. Traditionally, each gene or mutation was tested individually in a targeted manner; the molecular method used was dependent of the type of mutation being tested and the diagnostic question. Targeted methods include Sanger sequencing for one or more exons, restriction fragment length polymorphism assay to target single nucleotides, or a hybridization method for small numbers of mutations. Sanger sequencing of entire genes, generally one exon at a time, was the standard method of sequencing and was relatively slow and labor intensive. The advent of massively parallel sequencing or NGS, which evaluates many genes at the same time, revolutionized testing. NGS can be performed by targeting a panel of genes, a whole exome, or a whole genome. The large increase in efficiency of scale for providing information rapidly demonstrated NGS' power for diagnostic purposes,

particularly when multiple genes are associated with a clinical phenotype. Sanger sequencing is still a cost-effective approach for targeted analysis, such as a known familial mutation or for confirmation of a mutation found through NGS.

However, not all mutational mechanisms lend themselves to standard NGS methods, especially repeat expansion diseases with large repeated sequences such as *C9orf72*. For this mutational mechanism, a targeted analysis using repeat-primed PCR is typically used. In addition, large deletions or copy number variations are not reliably detected by all NGS methods. For these targeted methods or array-based methods are needed.

Genetic testing for a disease phenotype, such as FTD and AD, requires knowledge of the associated genes and the types of causative mutations to ensure the testing method(s) selected will detect the relevant mutations allowing for clinical interpretation. Each genetic test has limitations which must be considered in the ordering and interpretation of genetic testing results.

2.4 Clinical genetic counseling and testing issues for AD and FTD produced by NGS

Genotype-phenotype correlation studies highlight how the phenotypes of dementia, particularly in the presence of a *C9orf72* expansion, can overlap thereby complicating diagnosis and prognosis. Although symptomatic treatment may not change, establishing a correct diagnosis is critical for determining eligibility for clinical trials and for genetic counseling of family members. Since the great majority of AD and FTD cases are not due to a definitive genetic etiology, genetic testing should not be considered standard of care. However, in the presence of a strong autosomal dominant family history or particular clinical presentation (e.g. very early onset or FTD/ALS), the option for genetic testing should be raised by the clinician [65]. Importantly, regardless of family history, all patients should be offered genetic counseling to any answer questions or concerns that the family may have. For many of these families, learning about their particular inheritance risk can lower anxiety and actually reduce the amount of testing ordered.

Standard diagnostic procedures now include biomarker testing to distinguish AD from other dementias, including amyloid imaging and measurement of β -amyloid and tau in cerebrospinal fluid (CSF). However, not all patients have access to these procedures and, even when they are performed, results may be inconclusive. Genetic testing potentially can clarify diagnosis. When deciding on the most efficacious course for genetic testing, diagnostic confidence, family history, and ability to pay for testing must be considered [66]. Diagnostic certainty may be improved by biomarker measurement but may not be an alternative because insurance will not cover it or it may not be available at the diagnostic site. A thorough family history of at least three generations is essential for establishing whether an autosomal family history is present and for clarifying diagnosis. For example, a patient who presents with memory complaints and family history of an early-onset amnesic disorder would strengthen a diagnosis of AD as opposed to a family history of a dementia with behavioral onset, which would hint at FTD. An even stronger indication of FTD would be a relative with ALS. Previous genetic testing on family members should be gathered.

However, clinical testing performed before 2011 would have missed mutations in *C9orf72* as well as in many of the rarer genes that are now associated with FTD. Ideally these families should be re-contacted and offered testing. However, the original patient may have died, and contact may have been lost. Additionally, patients may have been tested under a research protocol that did not permit re-contact.

Before the advent of NGS technology, single gene testing or disease specific sequencing panels (several genes sequenced at the same time) were performed based on probable diagnosis and family history. For financial reasons, testing frequently was performed sequentially. For example, with an autosomal dominant family history of early-onset AD, *PSEN1* would be tested first, then *APP*, then *PSEN2*. If these genes were negative, FTD genes might be tested. NGS allows for the simultaneous analysis of many genes at a lower cost per gene. However, NGS raises new issues, one of which is the generation of indeterminate results at an increased rate compared to older single gene technologies. Genetic variants identified by sequence analysis must be reviewed to determine their pathogenicity. A guideline for the interpretation and classification of sequence variants was published jointly by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. The guideline uses a risk score to classify variants into five categories based on available evidence: pathogenic, likely pathogenic, likely benign, benign, and variant of uncertain significance (VUS) [67]. A VUS is a variant for which there is not enough evidence to classify as pathogenic or as benign. The more genes that are tested, the more likely it is to find one or more VUS. Although polymorphisms were also revealed when Sanger sequencing was the common methodology, the greater number of genes analyzed in NGS panels or WES increases the risk of detecting one or more VUS. While the significance of a VUS may be clarified by testing additional family members, family members are not always available. Therefore, VUS and any unclear genetic analysis result can raise genetic counseling dilemmas. Finding another definitive pathogenic mutation in a disease-associated gene reduces, but does not eliminate, the chance that a VUS is associated with the disease in the family. This complication stems from the rare discovery that mutations in 2 different genes can co-exist in the same individual. Examples of this include, *C9orf72/GRN*, *C9orf72/MAPT*, *C9orf72/SQST1*, *C9orf72/TARDP* [56, 68, 69].

A dementia gene panel NGS test may be ordered for a patient with an autosomal dominant family history. Testing laboratories do not necessarily include the same genes on their panels. Because testing techniques are different, *C9orf72* may not be included on a panel and should be ordered separately. A suggested testing workflow algorithm (Figure 1) is to first test for an expansion in *C9orf72* and then, if negative, reflex to an NGS gene panel possibly followed by duplication/deletion (dup/del) testing of specific genes such as *APP*. Typically if an expansion is discovered, further testing is cancelled. This stepwise testing algorithm is the most cost-effective process; however, by not running the full gene panel, a second mutation in another gene may go undiscovered. Likewise, running a smaller, disease-specific panel, (e.g. a panel containing only AD-related genes) may fail to reveal an unexpected gene. Therefore, in clinical settings, patients should be counseled about the benefits and limitations of each type of test. When possible (insurance coverage or ability to pay), patients should be given the option of selecting a complete panel. Unfortunately, not all laboratories certified under the Clinical Laboratory Improvement Amendments of 1988

(CLIA '88) perform all relevant tests. The clinical presentation and specific family history may help to dictate what testing to pursue, but even with a thorough neurological workup, varying genotype-phenotype associations as well as disease phenocopies can lead to unexpected results. Sha et al. reported finding a *C9orf72* expansion in a 64-year-old man with a positive amyloid scan, and diagnosis of AD [70].

A strong family history suggesting an inherited disorder is an important trigger for ordering genetic testing; however, testing should also be considered in apparent sporadic cases since sporadic mutations, particularly in *C9orf72*, have been reported [71]. Presenting the possibility of a genetic etiology may provoke unnecessary worry. Clinicians must balance possible unwarranted anxiety with the patient's right to elect whether to pursue testing. The specific disease presentation may clarify whether to pursue testing (e.g. testing would be inappropriate for a sporadic case of classic LOAD, but relevant for ALS). Genetic counseling can be offered to assist patients and their families with the decision to test.

3. Conclusions and best practice for genetic testing for AD and FTD

Determining the appropriate algorithm for diagnostic genetic testing is dependent on clinical phenotype, biomarker testing, and family history. A three-generational family history should be taken which includes onset symptoms and ages of any neurological or psychiatric disorder and ages of death. Based on this information, the likelihood of finding a mutation can be assessed [65, 72]. Additionally, any prior genetic testing or autopsy within the family should be documented, preferably with written records. The existence of a known pathogenic mutation in a family member allows single mutation targeted analysis. Availability of an affected relative's autopsy may guide testing since underlying pathology correlates well with gene mutation. However, pathological techniques have changed significantly over the past few decades. Prior to 2006, TDP-43 staining did not exist [73]. At that time, non-tau ubiquitin-positive FTD was reported as dementia lacking distinctive histology. Nevertheless, a pathological diagnosis of AD in a family with multiple family members with similar phenotype to the proband will enable genetic testing to focus on AD-associated genes, whereas a report of a tauopathy might point to testing for *MAPT* mutations and TDP-43 pathology would suggest targeting *GRN* and *C9orf72* and other genes.

After evaluating the available information, the algorithm for genetic testing can be formulated (Figure 1). As suggested above, the clinician should strive to narrow the number of genes being tested. WES should not be ordered unless, in the presence of a definitive family history or unusual clinical presentation, an NGS panel is negative (Figure 1). Otherwise, WES is unlikely to reveal a causal mutation and may add to uncertainty with the identification of one or more VUS. Unlike with childhood diseases, parents and older relatives of patients with adult-onset neurodegenerative diseases are often unavailable for testing to help clarify the significance of VUS. In some cases, exome sequencing can help uncover a different disease diagnosis than that which was initially suggested based on presenting phenotype due to the extensive clinical overlap of neurodegenerative disease phenotypes.

All families should be offered genetic counseling to inform them about the reasons for and implications of testing, and their benefits and limitations of different avenues of testing, and to guide decision making. Patients must be informed about whether their insurance will cover testing and if not about the cost of the different tests.

As data is collected over time in shared databases such as ExAC, variants now classified as uncertain may be reclassified. Additionally, more information on the penetrance of different variants and the existence of genetic phenomena such as anticipation will be available. Even now, well-established autosomal dominant genes such as *PSEN2*, *GRN* and *C9orf72* are known to be less than fully penetrant. Large research studies such as the Dominantly Inherited Alzheimer's Network (DIAN), Longitudinal Evaluation of Familial Frontotemporal Dementia (LEFFTDS), and Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) will add to existing penetrance data. Information from these large studies combined with experience gained from increasing clinical application of NGS technologies for the diagnosis and counseling of neurodegenerative disease patients will undoubtedly improve the ability to counsel patients and families about their genetic risks and to navigate the many options for genetic testing.

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Figure 1: Algorithm for genetic testing for Alzheimer's disease and frontotemporal dementia (AD: Alzheimer's disease; FTD: frontotemporal dementia; ALS: amyotrophic lateral sclerosis; NGS: next generation sequencing)