

The clinical utility of gene testing for Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is the largest cause of dementia, affecting 35.6 million people in 2010. Amyloid precursor protein, presenilin 1 and presenilin 2 mutations are known to cause familial early-onset AD, whereas apolipoprotein E (APOE) ϵ 4 is a susceptibility gene for late-onset AD. The genes for phosphatidylinositol-binding clathrin assembly protein, clusterin and complement receptor 1 have recently been described by genome-wide association studies as potential risk factors for late-onset AD. Also, a genome association study using single nucleotide polymorphisms has identified an association of neuronal sortilin related receptor and late-onset AD. Gene testing, and also predictive gene testing, may be of benefit in suspected familial early-onset AD however it adds little to the diagnosis of late-onset AD and does not alter the treatment. We do not recommend APOE ϵ 4 genotyping.

Introduction

Alzheimer's Disease International estimates that in 2010 35.6 million people will have dementia.¹ Alzheimer's disease (AD), a disease first described by Alois Alzheimer in 1906, is the largest cause of dementia.^{2,3} AD typically affects those aged over 65 years (late-onset AD) but can also affect those younger than 65 years (early-onset AD).^{4,5} AD is an insidious neurodegenerative disease, beginning with self-reported short-term memory problems and progressing until total loss of cognitive function and death.² Current AD medications have a minor symptomatic effect and do not prevent its progression. The brains of AD patients are characterized by extracellular plaques of amyloid-beta ($A\beta$) and intracellular neurofibrillary tangles containing hyperphosphorylated tau protein.⁶ The process by which these plaques and tangles cause AD is not perfectly understood, however three genes were identified to be involved in familial early-onset AD in the mid-1990s, namely amyloid precursor protein (APP) and the presenilins (PSEN1 and PSEN2) (Table 1).^{6,7} Mutations in these genes only account for a very small percentage of AD patients,⁴ and the search for other potential causes of AD continued. The apolipoprotein E

(APOE) ϵ 4 allele has been identified as a major risk factor for the development of late-onset AD, but not all those who possess the allele develop AD and not all who have AD possess the allele.⁴ A genome association study using single nucleotide polymorphisms (SNPs) has identified an association of neuronal sortilin related receptor (SORL1) and late onset AD.⁸ More recently genome-wide association studies (GWAS) have identified some novel genes associated with AD: clusterin (CLU), complement receptor 1 (CRI), and phosphatidylinositol-binding clathrin assembly protein (PICALM).^{3,6,7} This paper will examine the clinical utility of genetic testing in AD in light of recent discoveries.

Familial early-onset Alzheimer's disease

Familial early-onset AD is a very rare disease which occurs when a highly penetrant gene mutation is inherited in an autosomal dominant pattern. As mentioned above, mutations in APP, PSEN1, and PSEN2 have been identified as causes of familial early-onset AD.⁴ Genetic testing may be of benefit in this situation as the identification of the specific mutation in affected family members will confirm the diagnosis of familial early onset AD.⁴ A similar, and well established, example of an autosomal dominant neurodegenerative disorder is Huntington's Disease (HD). Research conducted with HD families is the basis for many of the recommendations regarding genetic testing for autosomal dominant neurodegenerative disorders.⁴ As with HD, predictive gene testing may be requested by unaffected family members in a familial early-onset AD as knowledge of carrier status may have implications for reproduction.⁴ Furthermore, preimplantation genetic diagnosis may be an option if a known carrier would like to ensure they do not pass the mutation onto future offspring.⁴ At least one instance of this has been reported in the literature, with a healthy child born.¹⁰

Late-onset Alzheimer's disease

Late-onset AD is the most common form of AD, and is usually sporadic. However, as already mentioned, some alleles have been identified to increase the risk of developing late-onset AD. APOE ϵ 4 is a well-established risk factor for AD, and is associated with a four-fold risk of developing the disease.^{4,6,11} Since 2007 a number of GWAS have been performed confirming that APOE ϵ 4 is the most significant gene associated with late-onset AD.¹²⁻¹⁴ Other identified genes have only a small effect on the risk of developing AD. SORL1 has been associated with late-onset AD through using SNPs, and PICALM, CLU, and CRI have recently been identified by GWAS as novel risk factor loci.^{3,6-8,13,14} GRB2-associated

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binding protein 2 (GAB2), bridging integrator 1 (BIN1), exocyst component 3-like 2 (EXOC3L2) and methylenetetrahydrofolate dehydrogenase (NAPD⁺ dependent) 1-like (MTHFD1L) have been identified as associated with the development of AD, but have been replicated with mixed results.¹⁵⁻¹⁷ Other possible AD genes can be found online (www.molgen.ua.ac.be/ADMutations and www.alzgene.org).

Unlike familial early-onset AD, the presence of these genes does cause AD, but are rather susceptibility genes. Whilst genetic testing can readily identify the presence or absence of these susceptibility genes, this is of little clinical or diagnostic benefit.^{4,18} A patient may carry the APOE ϵ 4 allele and not develop AD, or may develop AD without the APOE ϵ 4 allele.¹⁹

Recommendations for gene testing in Alzheimer's disease

Diagnosis of Alzheimer's disease

The diagnosis of AD can be difficult and clinical expertise is required to distinguish it from other neurodegenerative disorders. Appropriate clinical guidelines, modified in the modern era and including clinical history, neurological examination, imaging in the form of MRI and PET, and genetic testing in appropriate individuals, should be followed.^{20,21} Currently, the diagnosis of AD should not rely solely on genetic testing, but should rather be built from a number of resources.

Familial early-onset Alzheimer's disease

A positive family history of early-onset AD with an autosomal dominant inheritance pattern is strongly suggestive of familial early-onset AD. A patient with suspected familial early onset AD should be referred to a clinician with an interest in familial dementia and experience in genetic neurodegenerative disorders to confirm the diagnosis.⁴ Genetic testing may be carried out, with the patient's permission, to determine if there are mutations in APP,

PSEN1, or PSEN2 which would confirm the diagnosis of familial early-onset AD.^{4,9} If a demented person has a PSEN1 mutation and has a MRI scan that is supportive, then the diagnosis is AD. DNA banking, for future analysis, should be provided as an option for those who do not currently want a test or those who may lack a known mutation.⁴

Predictive gene testing for mutations in APP, PSEN1, or PSEN2 in healthy adults should be conducted in a setting of adequate genetic counseling and confidentiality. This should consist of counseling regarding the purpose of performing testing, the meaning of positive or negative results, the implication of results for the patient and their family, alternative options, the benefits and risks, and reassurance that care will not be withdrawn as a result of not undergoing testing.^{4,9} Despite the lack of a cure for familial early-onset AD, there are some benefits to undergoing predictive gene testing. These include life-planning (e.g. whether or not to reproduce) and social planning (e.g. financial and social support).^{4,9} The risks of predictive gene testing include depression, disruption to family and breach of confidentiality, which could lead to social stigmatization, job or health insurance loss in those found to have the mutation.⁹ For those without a mutation the risks include depression and *survivor's guilt*.⁹ Genetic information is both inherently individual and also shared by a family; therefore there may be some dilemmas when one individual would like to undergo predictive gene testing when their parent or monozygotic twin does not wish to know their genetic status.^{4,9} It is best that an agreement be reached through adequate counseling; however if agreement cannot be reached then predictive gene testing should be carried out provided the parent or twin has time to protect against inadvertently learning the outcome.⁹

Late-onset Alzheimer's disease

For patients with sporadic late-onset AD genetic testing for APOE ϵ 4, SORL1, CLU, CRI, or PICALM is not recommended as it does not provide clinically useful information. These risk factor genes do not improve the sensitivity of specificity of the diagnosis, nor do they alter the treatment.^{4,18} Predictive gene testing for these risk factor genes is also not recommended as there is currently no potential for prevention or early-intervention. Knowledge of APOE ϵ 4 status in adults with a parent with Alzheimer's disease did not result in significant short-term psychological distress according to the REVEAL study conducted by Green and colleagues.²² However research conducted by Chilibeck and colleagues demonstrates that this knowledge is assimilated into pre-existing beliefs about family susceptibility and the complexity of disease causation.²³ Furthermore, knowledge of the absence of APOE ϵ 4 did not

dissuade some from the belief that they will develop AD.²³ Patients already have their own beliefs of their susceptibility and knowledge of genetic risk, delivered with counseling, does not profoundly change their beliefs.²³ This illustrates that there is little benefit to knowledge of APOE ϵ 4. After all, a lack of risk factor genes holds no guarantee that the individual will not develop late-onset AD and conversely the presence holds no guarantee the individual will develop the disease.

Education, counseling and support

As always, genetic testing should be carried out in a setting of confidentiality, education, counseling, and support from a multidisciplinary team with expertise in genetic neurodegenerative disorders.^{4,9} The patient and their family should understand the risks and benefits, their alternative options and the implications of the results.^{4,9} In the instance that the patient is demented to the extent that they are unable to give informed consent and family members are not united in the decision to undergo genetic testing, then it should not be performed until a consensus is reached. Genetic counseling, as part of multidisciplinary care, should be provided to assist resolution.

Laboratory accreditation and DNA result disclosure

DNA testing for patients with suspected AD should always take place in an appropriately accredited laboratory. Whilst the accreditation requirements vary in each nation, the testing should be carried out in a reputable laboratory with quality controls in place to ensure accuracy.^{4,9,24} The US NIH Genetic Testing Registry, which is expected to become operational in the near future, will address the utility and availability of genetic tests and make this information publicly available, however it will be relying on genetic testing providers to voluntarily submit information.²⁵ The success of this registry will become evident in time. Direct to consumer (DTC) genetic testing is not recommended for either familial AD or sporadic AD gene testing. As a result of a report from the US Government Accountability office, the US Food and Drug Administration has recently notified a number of DTC service providers that their products meet the definition of a medical device based on the manufacturer's claims about test results, and therefore now need to be proven to be safe, accurate and effective.^{26,27} Up to now these tests had been unregulated and alarmingly one manufacturer had planned to make their test available through a pharmacy chain.²⁶ The risks of DTC genetic testing lie in decision making as a result of the genetic test.^{9,26} Also there have been instances of consumers receiving results belonging to someone else.²⁸ This highlights the importance of laboratory regulation and

Table 1. The genes associated with familial and sporadic Alzheimer's disease.

Familial	Sporadic
APP	APOE ϵ 4
PSEN 1	CLU
PSEN 2	CRI
	PICALM
	SORL1

genetic counseling as part of the testing process. To ensure confidentiality, the results of genetic testing should go directly to the clinician who requested the test.⁴ They can then be delivered to the patient and their carer under strict confidence, with assistance from genetic counselors.^{4,9} These counselors should continue follow-up with the patient to reduce the risk of adverse reactions, such as psychiatric hospitalization and suicide attempts.⁴ This method as has been successful with Huntington's disease.²⁹

Conclusions

Genetic testing has a role in the diagnosis of familial early-onset AD, however it adds little to the diagnosis of sporadic AD. The use of predictive gene testing for people at risk of familial early-onset AD may be beneficial, however it is not recommended for risk-factor genes, including APOE ϵ 4, particularly as there is no known preventative or curative measure available. Any genetic testing should always be conducted in a setting of adequate genetic counseling in a regulated and reputable laboratory. Confidentiality of results should always be assured to the patient.

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