

Predicative Genetic Testing for Alzheimer's Disease

Tih-Shih Lee, ¹MD, PhD, FRCP(C)

Alzheimer's disease (AD) is one of the most common types of dementia worldwide and it is of tremendous concern to individuals and society at large. Current diagnostic criteria are based on the Diagnostic and Statistical Manual for Mental Disorders, 5th Edition (DSM-5), and they are coded as major neurocognitive disorders due to AD.¹ Risks of developing AD are associated foremost with genetic factors and age. Other contributing factors may include sex, education level, concurrent medical problems and lifestyle. Members of the general population are at an approximately 10% to 12% risk of developing AD in their lifetime, while those with a first-degree relative who has AD have a 2- to 4-fold increase in risk.² Risks are also much higher for those who have a family history of autosomal dominant AD. Therefore, asymptomatic individuals, especially those who have relatives with AD, may seek predicative genetic testing because of their concerns about early cognitive symptoms, advance planning for financial or personal affairs, and relief from anxiety.³

Autosomal dominant AD is a rare form of AD and estimated to be 1% to 5% of all AD cases. It usually manifests before the age of 60, and is considered a form of early onset AD (EOAD). Currently there are only 3 known deterministic genes in which mutations are associated with autosomal dominant AD — amyloid precursor protein (APP), presenilin 1 (PSEN 1) and presenilin 2 (PSEN 2). These mutations have close to complete penetrance but variable expressivity, i.e. virtually anyone who possesses 1 mutant allele will eventually get the disease, but severity may vary even between members of the same family with the same mutation.⁴ The risk of an individual who has a parent with autosomal dominant AD of getting the disease is 50%.

Far more common is late onset AD (LOAD). Despite massive efforts to uncover the genetic basis of LOAD, the only gene associated with AD that has been consistently

replicated in multiple genome-wide association studies is apolipoprotein E (APOE). Others reported in various studies include *BINI*, *CLU*, *PICALM*, *CR1* and *TOMM40*. Only APOE will be discussed further as it is the only one with any risk data. The APOE gene encodes a protein involved in cholesterol transport and exists in three isoforms ($\epsilon 2$, $\epsilon 3$, $\epsilon 4$), differing only by single amino acid substitutions.⁵ Unlike the genetic mutations in autosomal dominant AD, APOE $\epsilon 4$ is a susceptibility gene, i.e. one that increases the risk of getting AD. There have been many publications concerning the extent of increased risk of possessing the APOE $\epsilon 4$ allele. The degree of risk varies depending on whether the individual carries one or two $\epsilon 4$ alleles. The lifetime risk of contracting AD may increase from 9% in $\epsilon 4$ -negative persons to 29% for carriers of a single $\epsilon 4$ allele.⁶ Compared with $\epsilon 3/\epsilon 3$ individuals, the odds ratio (OR) of developing AD have been estimated to be 3.2 (95% CI, 2.9 to 3.5) and 11.6 (95% CI, 8.9 to 15.4) for carriers of 1 or 2 $\epsilon 4$ alleles, respectively; and the appearance of AD symptoms in $\epsilon 4$ carriers may be accelerated by 1 to 2 decades.⁷ The conversion from mild cognitive impairment (MCI) to incipient AD has been shown to be expedited.⁸ Several studies have also suggested that the presence of an $\epsilon 2$ allele may play a protective role against developing AD.^{9,10} Other studies about the effects of the $\epsilon 4$ allele suggest that it influences the age at which AD occurs, rather than the overall lifetime risk for AD.^{11,12} Since the possession of the $\epsilon 4$ allele is neither necessary nor sufficient to cause AD, the sensitivity and specificity of APOE genotyping are insufficient for definitive AD diagnosis or prognosis. It is also difficult to convey such probabilistic risk effectively since the risk is usually reported as a population-based OR, which is difficult to translate into meaningful figures for individual counselling.¹³ Moreover most of the studies are on individuals of European or African-American descent and may not be generalisable to other populations.

¹Neuroscience and Behavioural Program, Duke-NUS Graduate Medical School, Singapore

Address for Correspondence: A/Prof Tih-Shih Lee, Neuroscience and Behavioural Program, Duke-NUS Graduate Medical School, 8 College Road, Singapore 169857.

Email: tihshih.lee@duke-nus.edu.sg

However, potentially modifiable AD risk factors have been shown to be affected by the presence or absence of the APOE $\epsilon 4$ allele.¹⁴ Knowing one's APOE status may prompt individuals to make lifestyle changes to reduce their risk. Besides, individuals who seek APOE testing for AD commonly cite disease risk reduction as a prime motivator.¹⁵ This is further supported by findings from the seminal Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study. This study showed that individuals who were informed of a high AD risk estimate were more likely to modify health behaviours aimed at diminishing the perceived risk even if the effectiveness of the activities were not proven.¹⁶ The study also showed that disclosure of $\epsilon 4$ -positive status does not appear to confer psychological or social harm to asymptomatic individuals seeking personal AD risk estimation. The authors concluded that the identification of modifiable AD risk factors and the advent of effective interventions may enable clinicians to identify at-risk individuals who may thereby benefit maximally from such interventions.¹⁶⁻¹⁸

At present, the American College of Medical Genetics (ACMG), in its Practice Guidelines (2011), recommends that predictive testing be only done at the request of the individual if there is known family mutation in PSEN1, PSEN2 or APP.² This would occur in the context of pretest genetic counselling, risk evaluation, neurological and psychiatric evaluations, post-test results counselling and follow up. This protocol is similar to the Huntington Disease (HD) Society of America's Guidelines for Genetic Testing for Huntington Disease.¹⁹

Moreover the Practice Guidelines state that genetic testing for susceptibility loci (e.g. APOE) is not clinically recommended due to limited clinical utility and poor predictive value.² However, if an individual wishes to pursue testing, it can be done at the discretion of the clinician, who should still follow the above HD guidelines. Emphasis should be placed on the probabilistic nature of the results: individuals with 1 or 2 copies of the $\epsilon 4$ allele may not necessarily develop AD and those without any $\epsilon 4$ may still develop the disease. The clinician should also explore the motives and considerations for pursuing genetic testing, and also how the results, whether positive or negative, would impact their psyche, life plans and relationships.

AD, at this point of time, can neither be prevented nor cured, and the medical rationale to determine APOE genotype has been limited thus far. However, these recommendations may change in the future if we gain more knowledge into the pathogenesis of AD and the role of susceptibility genes, and if disease modifying interventions become available.

REFERENCES

1. American Psychiatric Association. Major or mild neurocognitive disorder due to Alzheimer's disease. In: Diagnostic and statistical manual of mental disorders. 5th edition. Washington: American Psychiatric Press, 2013.
2. Goldman JS, Hahn SE, Catania JW, LaRusse-Eckert S, Butson MB, Rumbaugh M, 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.
3. Steinhardt EJ, Smith CO, Poorkaj P, Bird TD. Impact of DNA testing for early-onset familial Alzheimer disease and frontotemporal dementia. *Arch Neurol* 2001;58:1828-31.
4. Campion D, Dumanchin C, Hannequin D, Dubois B, Belliard S, Puel M, et al. Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. *Am J Hum Genet* 1999;65:664-70.
5. Zannis VI, Kardassis D, Zanni EE. Genetic mutations affecting human lipoproteins, their receptors, and their enzymes. *Adv Hum Genet* 1993;21:145-319.
6. Seshadri S, Drachman DA, and Lipka 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;52:1074-9.
7. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261:921-3.
8. Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Berry-Kravis E, Bennett DA. The apolipoprotein E epsilon4 allele and incident Alzheimer's disease in persons with mild cognitive impairment. *Neurocase* 2005;11:3-7.
9. Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC Jr, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nat Genet* 1994;7:180-4.
10. Saunders AM. Apolipoprotein E and Alzheimer disease: an update on genetic and functional analyses. *J Neuropathol Exp Neurol* 2000;59:751-8.
11. Khachaturian AS, Corcoran CD, Mayer LS, Zandi PP, Breitner JC, Cache County Study Investigators. Apolipoprotein E epsilon4 count affects age at onset of Alzheimer disease, but not lifetime susceptibility: The Cache County Study. *Arch Gen Psychiatry* 2004;61:518-24.
12. Meyer MR, Tschanz JT, Norton MC, Welsh-Bohmer KA, Steffens DC, Wyse BW, et al. APOE genotype predicts when—not whether—one is predisposed to develop Alzheimer disease. *Nat Genet* 1998;19:321-2.
13. 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;6:192-6.
14. Patterson C, Feightner J, Garcia A, MacKnight C. General risk factors for dementia: a systematic evidence review. *Alzheimers Dement* 2007;3:341-7.
15. Christensen KD, Roberts JS, Uhlmann WR, Green RC. Changes to perceptions of the pros and cons of genetic susceptibility testing after APOE genotyping for Alzheimer disease risk. *Genet Med* 2011;13:409-14.
16. Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, Green RC, REVEAL (Risk Evaluation and Education for Alzheimer's Disease) Study Group. Genetic risk assessment for adult children of people with Alzheimer's disease: the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study. *J Geriatr Psychiatry Neurol* 2005;18:250-5.
17. Green RC, Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, Brown T, et al. Disclosure of APOE genotype for risk of Alzheimer's disease. *N Engl J Med* 2009;361:245-54.
18. Marteau TM, Roberts S, LaRusse S, Green RC. Predictive genetic testing for Alzheimer's disease: impact upon risk perception. *Risk Anal* 2005;25:397-404.
19. International Huntington Association (IHA) and World Federation of Neurology (WFN) Research Group on Huntington's Chorea. Guidelines for the molecular genetics predictive test in Huntington's disease. *Neurology* 1994;44:1533-6.