# Chapter 7
# Alzheimer Disease

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With a prevalence of 5.2 million people in the USA, Alzheimer disease (AD) is the most common dementia and the most common of all neurodegenerative diseases. It is estimated that the incidence will double by 2050 [1]. Although AD is more common among women, this difference is largely due to length of life. The disease is found around the world in all ethnic groups. In the USA, African-Americans and Hispanics are at greater risk for AD, probably because of their increased risk of other diseases such as hypertension and diabetes [1].

Of those people with AD, approximately 200,000 are under the age of 65. It is this group with early-onset AD that is more likely to have a familial form of the disease. Although the genetic burden of AD is likely to be quite large, overall less than 1 % of all AD is due to autosomal dominant genes. Regardless of the cause, the definitive diagnosis of AD is made at autopsy [1].

## 7.1 Clinical Presentation

Alzheimer disease typically has an insidious onset with forgetfulness demonstrated by repeating conversation and questions, misplacing items, forgetting events, getting lost, having trouble with calculations such as making correct change or balancing a checkbook, and having word-finding problems. However, diagnostic criteria for Alzheimer disease are in a state of flux largely due to advances in

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neuroimaging and CSF biomarkers, as well as in clinical and pathological assessment. Atypical presentations of AD have been described where patients demonstrate relatively preserved memory but autopsy reveals AD pathology. Whereas the existing diagnosis of AD required impairment in memory and another cognitive domain, the proposed revised criteria state that there must be a gradual onset of symptoms with progression to cognitive impairment in any domain which impairs the activities of daily living, and that other forms of dementia are largely ruled out [2–4]. Atypical AD presentations include mood/behavior change, language impairment resulting in a progressive aphasia, or cortically derived vision problems resulting from posterior cortical atrophy. About a third of people with early-onset AD have atypical features [5].

As AD progresses, all areas of cognitive function will be affected. In early to middle stages of the disease, short-term memory is primarily affected. Later, long-term memory will become impaired. Eventually the ability to recognize faces, including family, will be lost. People with middle to late stage AD may have psychiatric symptoms such as depression, agitation, delusions, and hallucinations. They will have poor judgment, may become disoriented to time and place, lose language and the ability for self-care, and become incontinent. Many people develop parkinsonian features that can lead to an increased risk of falling. Myoclonus and seizures also can develop. Ultimately, patients will be bedridden. Disease duration is variable with the mean being approximately 12 years from onset (6 years from clinical presentation) [6]. The ultimate cause of death is likely to be an unrecognized infection, aspiration pneumonia, or dehydration.

People with AD and their caregivers often become progressively isolated. The need for maintaining a good quality of life for both patient and caregivers should be addressed by healthcare providers including genetic counselors, and appropriate resources should be given.

## 7.2 Diagnosis

In addition to the neurological history, AD is diagnosed by meeting the clinical criteria and ruling out infection, paraneoplastic disease, hormonal, and metabolic causes of dementia through routine laboratory testing and lumbar puncture. A quick neuropsychological screen that can be performed during a clinical visit is the Mini Mental Status Exam (MMSE). However, much more extensive neuropsychological testing is necessary to reveal the type and extent of cognitive impairment. Additionally, the diagnostic process includes neuroimaging, neuropsychological testing, and often a lumbar puncture to test the CSF markers, β-amyloid and tau proteins. In typical AD, MRIs show reduced hippocampal volume and temporal–parietal atrophy. Functional imaging shows reduction in metabolism and blood flow in the temporal–parietal cortex [3]. PET imaging using amyloid staining can assist with diagnosis, but as of this writing, has limited availability and is very expensive. The CSF biomarker profile increasing the likelihood of an AD diagnosis is low amyloid

$\beta_{42}$ and high total tau and phosphorylated tau. Neuroimaging and biomarkers as well as the neuropsychological profile help to improve diagnostic confidence, but are not foolproof. The finding of amyloid deposition in the brains of some elderly people who do not develop AD demonstrates how even amyloid neuroimaging is not 100 % predictive [4, 7]. Definitive diagnosis is autopsy with the pathological findings of amyloid plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein.

## 7.3 Treatment and Management

Treatment for Alzheimer disease is largely symptomatic. Although there are many clinical trials, at the present time available treatments include cholinesterase inhibitors ((donepezil, rivastigmine, galantamine) and an NMDA receptor antagonist, memantine. These compounds slightly improve cognition and function in some patients and may slow the rate of disease, but do not stop or cure it. Yet other patients gain no benefit from these medications and complain of side effects including gastrointestinal complications and sleep disorder [8]. Additionally, symptoms such as depression and agitation can be treated through antidepressants and antipsychotics.

Non-pharmacological treatment includes behavior modification, cognitive retraining, and stimulation activities. As social isolation is a problem for patients and their caregivers, support groups, daycare centers, and cultural programs designed for families living with dementia can be helpful. Organizations, such as the Alzheimer Association, run workshops for families on essential topics such as legal issues and handling difficult behaviors.

## 7.4 Genetics

Three genes have been linked to autosomal dominant AD: Presenilin 1 (*PSEN1*) at 14q24.3, Presenilin 2 (PSEN2) at 1q31-q42, and the amyloid precursor protein gene (*APP*) at 21q21.2. Of these, approximately 50 % of autosomal dominant AD has been attributed to *PSEN1*. Whereas several cases of asymptomatic *PSEN2* gene carriers have been reported, *PSEN1* and *APP* are thought to be 100 % penetrant (see Table 7.1).

Over 180 mutations have been described in *PSEN1*. Genotype/phenotype correlations exist for some mutations; however, phenotypic variation can be significant, even within families. Age of onset is usually in the 40s or 50s, although cases have been reported as young as the 20s and possibly as old as 70. Yet onset after 60 is highly unusual. In addition to typical Alzheimer type dementia, which begins with memory loss and/or visual/spatial problems, all areas of cognition can be affected including behavior, mood, executive function and language. Aphasia and

**Table 7.1** Genetic risk factors for Alzheimer disease

| Gene | Chromosome | Inheritance | Penetrance | Age of onset |
|---|---|---|---|---|
| *PSEN1* | 14q24.3 | Autosomal dominant | 100 % | 24–65 (AAO 45) |
| *PSEN2* | 1q31-q42 | Autosomal dominant | <100 % | 39–75 (AAO 54) |
| *APP* | 21q21.2 | Autosomal dominant | 100 % | 40s–60s |
| *APOE* | 19q13.2 | Autosomal dominant | Dosage related risk factor | Highly variable |

*AAO* average age of onset

behavioral/psychiatric symptoms are relatively common. Additionally parkinsonism, ataxia, myoclonus, seizures, and spastic paraparesis have all been reported [9, 10].

*APP* accounts for 10–15 % of autosomal dominant AD. Approximately 25 point mutations and duplications have been found in this gene [11]. In addition to cognitive impairment, the *APP* phenotype can include autonomic failure, seizures, behavioral changes, intracerebral hemorrhage, and cerebral amyloid angiopathy found on autopsy [12, 13].

*PSEN2* mutations are very rare. Approximately 15 mutations have been found in families of Volga German, Italian, and Spanish descent [14]. Age of onset is quite variable, and reduced penetrance has been reported. Seizures are also relatively common. Autopsy often reveals Lewy Body pathology (associated with Parkinson's disease) in addition to amyloid plaques and tau tangles, which accounts for occurrence of hallucinations [15].

Whereas less than 1 % of AD is due to these autosomal dominant genes, a significant portion is thought to involve genetic susceptibility factors. Heritability of AD is estimated at 58–79 % [16]. Through GWAS studies, numerous loci have been associated with risk. Of all the identified genes, only the apolipoprotein E gene (*APOE*) repeatedly shows a significant effect on risk.

*APOE* has 3 alleles, e2, e3, and e4. The e4 allele is associated with increased Alzheimer risk in a dose dependent manner, while the e2 allele is thought to be protective. A single e4 allele increases risk 2–3 times, whereas individuals with an e4/e4 genotype have about a 15-fold increase in lifetime risk [17, 18]. Risk is age-dependent and in e4/e4 individuals is about 50 % in males and 60 % in women by age 85. Individuals with e3/e4 have a 23 % (males)—30 % (females) risk by age 85 [18].

The significant increased risk conferred by this locus has led to interest in predictive testing. However, practice guidelines and position statements have not supported the use of *APOE* testing whether for diagnostic or predictive reasons [19]. This gene is neither necessary nor sufficient for developing AD. However, the REVEAL study has demonstrated that the select group of research patients who opt to hear their *APOE* status after genetic counseling generally cope well with their results. Yet a small minority (9 %) experienced depression up to a year after receiving results. Additionally the study showed that genetic counseling helped to reduce anxiety, perhaps by focusing on the difference between perceived risk and

objective risk [20]. *APOE* disclosure in the study group resulted in some behavioral change of *APOE* e4 positive as compared to negative individuals. Individuals testing positive were 4.75 times more likely to increase their use of vitamins and supplements (for which there is no good scientific basis), but not to increase exercise (which has been shown to be beneficial) [21]. Likewise, those testing positive were more likely to buy long-term care insurance [22]. Long-term care insurance is beneficial; however, since it is not covered by GINA, it should be purchased before testing to avoid any claim of insurance fraud or discrimination. *APOE* testing is available through DTC with or without counseling; thus, healthcare professionals may be asked questions about the implications of testing after it has already been performed.

In addition to *APOE*, other loci in combination contribute approximately 35 % to AD risk [23]. Of these, replication studies have confirmed *PICALM*, *BIN1*, *CLU*, *CR1*, where others including *SORL1*, *CD33*, *EPHA1*, *ABCA7* have been replicated in some populations [23–25]. More recent GWAS studies are concentrating on specific endophenotypes, such as age of onset or psychotic features, to increase significance of findings. Additionally, ethnic differences are being studied. The *ABCA7* gene seems to double the risk of AD in African-Americans [26]. Identification of these genes is important for a better understanding of Alzheimer disease pathways, even though testing for predictive purposes will not be productive.

## 7.5 Genetic Counseling Issues

Since interventions are not currently available, genetic testing for Alzheimer disease lacks clinical utility. Yet for some individuals or families, testing provides a better understanding of the family disease and closure to uncertainty. Genetic testing of an affected individual reveals the risk of disease for other family members, and therefore, the possibility of taking action on one's own risk. For many individuals, having this option increases anxiety. Thus, an important job of the genetic counselor is to prepare the family for possible backlash from extended family members. For many families, discussions prior to testing can prevent this backlash. Other families feel that they do not want to raise family anxiety until necessary or decide not to share results with others.

As mentioned in the introduction to this section, the genetic counselor should understand who and what is driving the interest in testing. If there is not family consensus and the patient is not fully competent, the genetic counselor can attempt a family meeting to reach consensus. Additionally, the family should be provided alternatives to testing, such as DNA banking and autopsy. If consensus cannot be reached, the counselor must accept the wishes of the legal power for healthcare decisions or next of kin.

In families for whom a mutation is unknown, the process of testing a person with AD is complicated by the existence of the three autosomal dominant genes as well as *APOE*. The strategy for testing is driven largely by whether insurance will cover

testing, as well as the ages of onset of family members. If cost is not an issue, the autosomal dominant AD panel can be ordered. If cost is of concern, testing should be done sequentially: first *PSEN1*, then *APP* (point mutations then duplications), and lastly, *PSEN2* (unless the family is of Volga German origin in which case *PSEN2* should be first). While whole exome or genome testing will expedite this process, results of unknown significance must be taken into account. The family needs to understand that a possible negative result for all three genes would reduce, but not eliminate, the risk of autosomal dominant inheritance. Testing for *APOE* is not recommended for diagnostic purposes. Although an *APOE* e4/e4 genotype might explain early onset and family clustering, this conclusion is not definitive. Likewise, in an autosomal dominant family, if the AD genes are negative, consideration should be given to testing for frontotemporal degeneration (FTD) and prion disease.

Once a mutation has been found in the family, other family members are eligible for testing, at which time the Huntington Disease protocol should be followed. As stated above, guidelines do not advocate *APOE* testing. However, patients may wish to proceed anyway. Genetic counseling should be offered, followed by testing at the physician's discretion. Some patients may present for counseling after DTC testing. These patients need to understand that carrying an e4 allele does not mean that they will definitely develop the disease, and conversely, that even if they do not carry an e4 allele, but have a positive family history, their risk only decreases slightly. They may wish to prepare for the possibility of developing AD.

## 7.6 Alzheimer Disease Case History (Fig. 7.1)

Mrs. L was a 59-year-old woman with a 3-year history of progressive cognitive impairment starting with memory loss. A complete neurological evaluation resulted in a diagnosis of probable Alzheimer disease. At the time of her initial evaluation, Mrs. L's Mini Mental Status Exam (MMSE) score was 24/30. Although she was very forgetful and had word-finding problems, she was still working. Yet, because of anxiety, she was having more problems at work. When the neurologist discussed applying for disability, she became agitated. The neurologist then referred Mr. and Mrs. L for genetic counseling about early-onset Alzheimer disease.

They presented at clinic with their 30-year-old daughter Maria. The counselor began the session by asking the family to explain the reason for referral. They understood that their doctor was concerned about hereditary AD. The family, especially the patient, seemed quite anxious during the initial discussion. A review of family history revealed that Mrs. L had 2 older sisters and a younger brother. Her oldest sister, now 62, developed memory problems at age 57. Their father, 2 out of 4 paternal uncles, and paternal grandmother died in their 70s with dementia. Mrs. L had been the primary caregiver to her father since her mother had died several years before his death. Mr. L reported that when Mrs. L started having symptoms, she

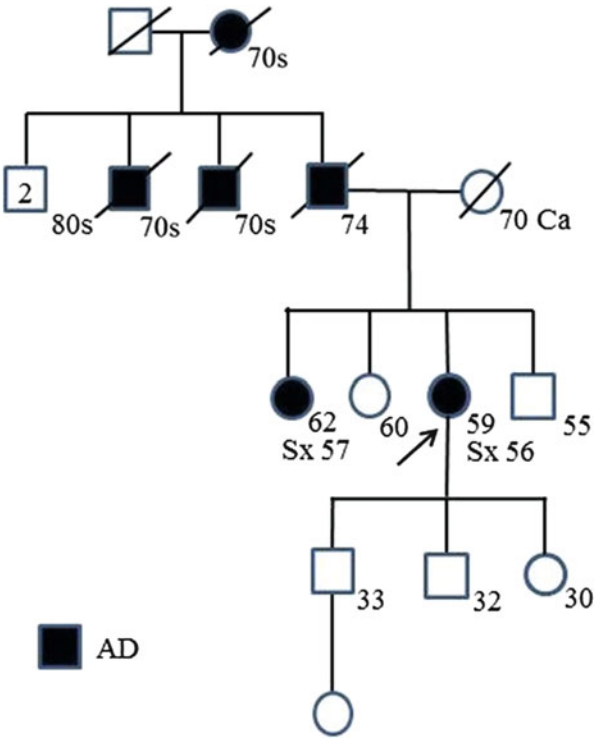


**Fig. 7.1** AD case history pedigree

became terrified that she would deteriorate to her father's state, and had refused evaluation until now. Mrs. L and her daughter both cried during this discussion.

The genetic counselor acknowledged how scary it is to be part of a family with a hereditary disease, especially when one has watched the dementia process. She asked Mrs. L if she wished to learn more about the inheritance of the disease and the possibility of testing for it. Mrs. L nodded yes. The counselor then discussed AD genetics and used Mrs. L's family tree to demonstrate autosomal dominant inheritance. She explained that it was possible to test for the 3 known autosomal dominant AD genes, and that if a mutation were found in any of them, it would prove the cause of the dementia in the family. Mr. L asked whether it would make any difference to her diagnosis or treatment. The counselor told him that testing would confirm diagnosis, but not change treatment. The discovery of a mutation would provide information for the children and other family members who might wish to find out whether they carry the mutation. It would also allow family members to enroll in a national research study looking at the earliest markers for the disease and/or a drug trial only open to families with a known mutation (DIAN-Dominantly Inherited Alzheimer Network). However, if no mutations were found, or the result was a variant of unknown significance, presymptomatic testing would not be possible. Maria said that she was newly engaged and would not want to discover her status at this time, but perhaps would in the future. She added that her

oldest brother already had a child and had disengaged himself from his mother and would not want to receive any information, but her other brother had gotten married recently and might be interested in results for reproductive options. At this point, Mrs. L became very agitated. When the counselor asked whether she was worried about her children, she cried that she did not want them or her husband to have to care for her, and she was terrified that they too would get the disease.

Again, the genetic counselor acknowledged Mrs. L's fears, but also asked her to consider how much research is being done on AD and how the world might be very different in 20 years. Both women nodded their heads and grinned. Maria said that she thought it was important for the family to find out everything they could. Mr. L agreed, but raised concerns about insurance discrimination. The counselor said that testing Mrs. L would not further affect her insurance since she was already diagnosed. She discussed GINA and suggested that anyone in the family who was interested in presymptomatic testing consider long-term care and/or life insurance prior to testing. She then asked whether the family would communicate results to other family members. She suggested asking people if they wished to know Mrs. L's results before any testing took place so that the family could honor the right not to know. However, she also discussed the difficulty of keeping family secrets. Once again Mrs. L became agitated because she feared her older son would get mad at her. Mr. L stepped in and said that he would handle it. The plan was to have a family meeting to discuss the genetic testing.

Discussion Questions

- How does diminished capacity influence a genetic counseling session and informed consent for genetic testing?
- How should consenting for AD testing take place in light of family disagreement?
- How do family secrets influence decisions to test?
- How much should a genetic counselor challenge optimism? Should hope for future treatment and prevention be a part of counseling?

Mr. and Mrs. L returned a month later, this time with their younger son, David. The men stated that they wanted Mrs. L to have genetic testing to provide information to this son and his wife, and perhaps to his sister, for future reproductive decisions. They said that the older son was not interested in testing, nor in learning the results, and that they would respect his choices. Mrs. L still seemed upset, and when asked if she wanted to be tested said, "I guess so." The counselor reminded her that testing was voluntary, and asked what was upsetting her. She said that she would test for David, but was scared that her children would get the disease. The counselor emphasized that knowledge of the genetic result would not alter her children's risk, but rather provide information enabling them to have choices. Mrs. L agreed to sign the consent and blood was drawn. Because she was found to be competent by a physician, no other signatures were necessary. Mr. and Mrs. L and David returned for results, which were positive for a *PSEN1* mutation. David said that he would like to arrange an appointment with the genetic counselor.

Several months later David contacted the counselor for an appointment. He and his wife were going to try to get pregnant so he wanted presymptomatic testing. The counselor suggested that both come for the appointment. In the office she reviewed Mrs. L's result and what it implied for David. She explored David's motivation for testing, which was largely for reproductive reasons. She then asked David whether he thought much about his risk. He denied being very concerned, saying that he was generally an optimistic guy. She asked him to imagine getting a positive result and how he would feel. Once again he reacted unemotionally, saying he would be fine. His wife, however, became tearful. When the question was addressed to her, she said she would be sad and scared about the future, but added that she thought David could cope with the information and that she could as well. Finally, she concluded that she would also want to have children sooner rather than later. The counselor reminded the couple that presymptomatic genetic testing would tell them if David carried the mutation, but not when he would develop symptoms. The family's average age of onset was in their 50s, which would, therefore, be the most likely age of onset for him as well. She also spoke about whether he would inform his relatives of his result. He said that he would not; that telling his mom would destroy her, and he did not want to burden his sister or father. They also spoke about the possibility of non-disclosing PGD and obtaining long-term care insurance prior to testing. David said that he would work to obtain the insurance.

The genetic counselor made several follow-up calls to David who continued to say he was pursuing long-term care insurance. On the second call he informed the counselor that he and his wife were expecting. He participated in the DIAN study and found the neuropsychological testing very stressful and then began to worry about his own cognitive ability. He never called back.

Discussion Questions

- What is the responsibility of a genetic counselor to follow up with patients who are considering testing? Does follow-up lead to pressure?
- Can giving "an out" like getting insurance be a good way for a genetic counselor to give a patient a legitimate excuse for not testing?
- How does a pregnancy influence the choice to get predictive testing for a late-onset disease?
- How does participation in a genetic family study influence the choice for clinical testing?

## 7.7 Resource for Patients

Alzheimer Association: www.alz.org/
Family Caregiver Alliance: www.caregiver.org
Alzheimer Disease Education & Referral Center (National Institute on Aging)
www.nia.nih.gov/Alzheimers/

## References


1. Alzheimer's Association. (2013). 2013 Alzheimer's disease facts and figures. *Alzheimer's & Dementia, 9*(2), 208–245.
2. American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4, text rev.th ed.). Washington, DC: American Psychiatric Association.
3. McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology, 34*(7), 939–944.
4. McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., et al. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 263–269.
5. Balasa, M., Gelpi, E., Antonell, A., Rey, M. J., Sánchez-Valle, R., Molinuevo, J. L., et al. (2011). Clinical features and APOE genotype of pathologically proven early-onset Alzheimer disease. *Neurology, 76*(20), 720–725.
6. Roberson, E. D., Hesse, J. H., Rose, K. D., Slama, H., Johnson, J. K., Yaffe, K., et al. (2005). Frontotemporal dementia progresses to death faster than Alzheimer disease. *Neurology, 65*(5), 719–725.
7. Devanand, D. P., Mikhno, A., Pelton, G. H., Cuasay, K., Pradhaban, G., Dileep Kumar, J. S., et al. (2010). Pittsburgh compound B (11C-PIB) and fluorodeoxyglucose (18F-FDG) PET in patients with Alzheimer disease, mild cognitive impairment, and healthy controls. *Journal of Geriatric Psychiatry and Neurology, 23*(3), 185–198.
8. Massoud, F., & Léger, G. C. (2011). Pharmacological treatment of Alzheimer disease. *Canadian Journal of Psychiatry, 56*(10), 579–588.
9. Bird, T. D. (1993). Internet. In R. A. Pagon, T. D. Bird, C. R. Dolan, & K. Stephens (Eds.), *GeneReviews*. Seattle, WA: University of Washington. 1999 Sep 24 [updated 2010 Dec 23].
10. *Alzheimer Disease & Frontotemporal Dementia Mutation Database*. http://www.molgen.ua.ac.be/ADMutations/
11. McNaughton, D., Knight, W., Guerreiro, R., Ryan, N., Lowe, J., Poulter, M., et al. (2012). Duplication of amyloid precursor protein (APP), but not prion protein (PRNP) gene is a significant cause of early onset dementia in a large UK series. *Neurobiology of Aging, 33*(2), 426.e13–21.
12. Basun, H., Bogdanovic, N., Ingelsson, M., Almkvist, O., Näslund, J., Axelman, K., et al. (2008). Clinical and neuropathological features of the arctic APP gene mutation causing early-onset Alzheimer disease. *Archives of Neurology, 65*(4), 499–505.
13. Wu, L., Rosa-Neto, P., Hsiung, G. Y., Sadovnick, A. D., Masellis, M., Black, S. E., et al. (2012). Early-onset familial Alzheimer's disease (EOFAD). *Canadian Journal of Neurological Sciences, 39*(4), 436–445.
14. Tanzi R. E. (2012). The genetics of Alzheimer disease. *Cold Spring Harbor Perspectives Medicine*, *2*(10), doi 2:a006296.
15. Jayadev, S., Leverenz, J. B., Steinbart, E., Stahl, J., Klunk, W., Yu, C. E., et al. (2010). Alzheimer's disease phenotypes and genotypes associated with mutations in presenilin 2. *Brain, 133*(Pt 4), 1143–1154.
16. Gatz, M., Reynolds, C. A., Fratiglioni, L., Johansson, B., Mortimer, J. A., Berg, S., et al. (2006). Role of genes and environments for explaining Alzheimer disease. *Archives of General Psychiatry, 63*(2), 168–174.
17. Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R., et al. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA, 278*(16), 1349–1356.

18. Genin, E., Hannequin, D., Wallon, D., Sleegers, K., Hiltunen, M., Combarros, O., et al. (2011). APOE and Alzheimer disease: A major gene with semi-dominant inheritance. *Molecular Psychiatry, 16*(9), 903–907.
19. Goldman, J. S., Hahn, S. E., Catania, J. W., LaRusse-Eckert, S., Butson, M. B., Rumbaugh, M., et al. (2011). Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genetics in Medicine, 13*(6), 597–605. Erratum in: *Genet Med,* 2011. 13(8), 749.
20. Ashida, S., Koehly, L. M., Roberts, J. S., Chen, C. A., Hiraki, S., & Green, R. C. (2010). The role of disease perceptions and results sharing in psychological adaptation after genetic susceptibility testing: The REVEAL Study. *European Journal of Human Genetics, 18*(12), 1296–1301.
21. Vernarelli, J. A., Roberts, J. S., Hiraki, S., Chen, C. A., Cupples, L. A., & Green, R. C. (2010). Effect of Alzheimer disease genetic risk disclosure on dietary supplement use. *American Journal of Clinical Nutrition, 91*(5), 1402–1407.
22. Zick, C. D., Mathews, C. J., Roberts, J. S., Cook-Deegan, R., Pokorski, R. J., & Green, R. C. (2005). Genetic testing for Alzheimer's disease and its impact on insurance purchasing behavior. *Health Affairs (Millwood), 24*(2), 483–490.
23. Naj, A. C., Jun, G., Beecham, G. W., Wang, L. S., Vardarajan, B. N., Buros, J., et al. (2011). Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nature Genetics, 43*(5), 436–441.
24. Hollingworth, P., Harold, D., Sims, R., Gerrish, A., Lambert, J. C., Carrasquillo, M. M., et al. (2011). Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nature Genetics, 43*(5), 429–435.
25. Seshadri, S., Fitzpatrick, A. L., Ikram, M. A., DeStefano, A. L., Gudnason, V., Boada, M., et al. (2010). Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA, 303*(18), 1832–1840.
26. Reitz, C., Jun, G., Naj, A., Rajbhandary, R., Vardarajan, B. N., Wang, L. S., et al. (2013). Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E ϵ4, and the risk of late-onset Alzheimer disease in African Americans. *JAMA, 309*(14), 1483–1492.