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·Minireview·

Alzheimer's disease: epidemiology, genetics, and beyond

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Abstract: Alzheimer's disease (AD) is an increasing epidemic threatening public health. Both men and women are susceptible to the disease although women are at a slightly higher risk. The prevalence of AD rises exponentially in elderly people from 1% at age of 65 to approximately 40%-50% by the age of 95. While the cause of the disease has not been fully understood, genetics plays a role in the onset of the disease. Mutations in three genes (*APP*, *PSEN1*, and *PSEN2*) have been found to cause AD and *APOE4* allele increases the risk of the disease. As human genomic research progresses, more genes have been identified and linked with AD. Genetic screening tests for persons at high risk of AD are currently available and may help them as well as their families better prepare for a later life with AD.

Keywords: Alzheimer's disease; amyloid precursor protein; presenilin; *APOE*

1 Introduction

Alzheimer's disease (AD) is a neurodegenerative disease featuring slow progressive dementia. The majority of clinically detectable dementia can be attributable to the disease[1,2]. Other common symptoms of AD patients include confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations[3]. Patients usually die of infection, malnutrition, pneumonia, or heart failure. Because the duration of the disease can be as short as one year and as long as 25 years with an average of eight to ten years, the social and economic costs are enormous. It is estimated that the American national direct and indirect annual costs of caring for individuals with AD are at least $100 billion and the loss to American business is $61 billion a year[4,5].

Although AD was identified one century ago in 1906, the cause of this devastating disease is largely still unknown. Therefore, no cure has been developed. Starting with the investigation of the AD cases in the patients with Down syndrome, we are now able to link about 5% of the disease with early onset to some gene defects. Researchers have also found a predictor gene (*APOE*) for those familial cases with late onset which accounts for 20% of AD. The remaining majority of the disease (75%) is still a puzzle[3].

The diagnosis of AD largely depends on clinical manifestations[6,7]. Pathologically, AD has two hallmarks formed by abnormal proteins toxic to nerve cells. Aβ-amyloid neuritic plaques are protein clumps outside the brain's nerve cells while the twisted protein strands, neurofibrillary tangles, can be found inside of cells[8,9]. The toxicity of these abnormal proteins gradually damages nerve cell function and eventually kills these cells resulting in a wide range of brain dysfunction featuring impaired memory, thinking and behavior, and ultimately death.

2 AD Epidemiology

AD is the most common neurodegenerative disease. Currently 4.5 million Americans have AD, more than double since 1980. The estimated number of Americans with AD by 2050 could reach from 11.3 million to 16 million, almost tripled the current patient number[10].

Age and gender are two leading risk factors of AD. Un-

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like many diseases, in AD women have higher risk than men. Age may be the most important factor in the illness. Although about one percent of individuals at the age of 65 are affected, the number increases quickly to about 50% for those people who are 95 or older[11]. It is possible that everybody may eventually have AD if he/she lives long enough before a cure is developed.

Family history is one more important risk factor. Compared with about 1% of risk for the whole population to develop AD by the age of 65, first-degree relatives of a single individual with AD in the family have about a 20% lifetime risk of developing AD[12,13]. When there is more than one AD patient in that family, the risk is further increased. For those offspring of early-onset familial AD, their risk of AD is even greater than 50%. Other risk factors associated with AD include overall health, head injury, heart disease, and diabetes. Although statistically they are important, none of them are good predictors of the incidence of the disease.

3 AD Genetics

Modern genetics is playing a critical role in understanding AD. Starting from the middle of 1980s, several genes have been linked to AD (Tab. 1)[14-21]. Among them, four genes (shown in bold) have direct relationship to the disease while the majority listed genes are uncertain yet. Missense mutations that alter a single amino acid and therefore gene function have been found in genes encoding amyloid precursor protein (APP), presenilin 1(PSEN1), and presenilin 2 (PSEN2),

Tab. 1 Genes associated with susceptibility to AD

Gene name	Chromosomal location	AD onset	Type of AD	Certainty of causing AD
ACE	17q23	Late	Sporadic	Uncertain
ACT	14q32.1	Late	Sporadic	Uncertain
APOE	**19q32.2**	**Late**	**Familial/Sporadic**	**Certain**
APOE promoter	19q32.2	Late/early	Sporadic	Uncertain
APP	**21q21.3–q22.05**	**Early**	**Familial**	**Certain**
AZM	12	Late	Sporadic	Uncertain
BChE	3q26.1–q26.2	Late	Sporadic	Uncertain
BH	17q11.1–q11.2	Late/early	Sporadic	Uncertain
catD	11p15.5	Late/early	Sporadic/Familial	Uncertain
CST3	20p11.2	Late	Sporadic	Uncertain
GAB2	11q14	Late	Sporadic	Uncertain
GST01/GST02	10	Late	Sporadic	Uncertain
IDE	10q23–q25	Late/early	Sporadic/Familial	Uncertain
LBP-1c/CP2/LSF	12	Late	Sporadic	Uncertain
LRP	12	Late	Sporadic	Uncertain
NOS3	7q35	Late	Sporadic	Uncertain
PSEN1	**14q24.3**	**Early**	**Familial**	**Certain**
PS1 promoter	14q24	Early	Sporadic/Familial	Uncertain
PSEN2	**1q31–q42**	**Early**	**Familial**	**Certain**
SORL1	11q23	Late	Sporadic	Uncertain
Tf C2	3q21	Late	Sporadic	Uncertain
TGF-β1	19q13.1–q13.3	Late	Sporadic	Uncertain
VLDL-R	9pter–p23	Late	Sporadic	Uncertain
α2M	12p	Late	Sporadic	Uncertain
5-HTT	17q11.1–q12	Late	Sporadic	Uncertain

Modified from Rocchi *et al.*[14]

which can cause early onset familial AD1, AD3 and AD4, respectively[22-25]. Furthermore, these types of ADs are inheritable with an autosomal dominant pattern[26,27], i.e. the risk to offspring of individuals with early-onset AD is 50% if a mutation is found in these three genes. The other gene, which is certainly associated with AD is *APOE*. It does not directly lead to the late-onset familial AD (AD2), but dramatically increases the risk of developing this disease for individuals over 65[28]. For those who carrying the *APOE4* allele, their risk of developing AD is 2-3 times greater than people who do not have this allele[29].

Currently, genome-wide search for AD is in full swing. Several potential AD associated genes[18-21] as well as loci are under investigation[30-41]. As the human genomic project processes, more and more genes are expected to be identified in the near future. Therefore, it is possible that the genetic causes for not only familial AD but also for many sporadic cases will be found.

4 From genetics to preventive medicine

AD is one of the world's greatest medical, social and economic challenges due to its impact on individuals, families and the health care system. Human genetic research brings us an entry point to understand and find a treatment for the disease. Nevertheless, it does not explain everything. Many other factors contribute to the development of AD. Several elegant twin studies have demonstrated that when one twin develops Alzheimer's, the other twin is at increased risk but does not necessarily develop the disease[42-44]. In addition, even in cases where both twins develop AD, the age of onset differs significantly[45]. The results of these twin studies clearly indicate that genetics and environmental factors work together to determine the development of AD. Although the early-onset familiar AD may be dominated by genetics, the majority of the disease is multi-factorial. For those cases with late-onset, they are likely the result of environmental factors on a predisposing genetic background[46]. We may know genetic causes of AD in a few years due to the progress of the human genomic project. Collecting information indirectly associated with AD such as environmental factors will be even more difficult but crucial to understand and prevent the disease.

Given the complexity of AD and its impacts on society, the hope to find the cause and then a cure is not the complete solution to this problem. While scientists in human genetics are making breakthrough in finding the genetic causes of AD, physicians and public health professionals should focus on preventive strategies. Providing the public with the necessary information to raise their awareness of the disease, furnishing patients, their families, friends, and relatives with genetic and medical knowledge, helping people to reduce risk factors related to AD, and treating patients with available medications will certainly prevent some cases from happening and improve many patients' quality of life.

Finding a preventive strategy for a specific disease is never an easy task. For the diseases like AD that have no cure yet, how to effectively utilize the knowledge to serve public is a real challenge. For example, the genetic consultation based on screening tests plays an important role in a preventive strategy for AD. However, this type of consultation in itself is controversial in the medical society. Currently, genetic tests are available in clinical or research laboratories for the four genes certainly associated with AD. However, *APOE* genotyping is neither fully specific nor sensitive. It may be helpful in the diagnosis of AD in symptomatic patients, but does not work well in predictive testing of asymptomatic individuals[47,48]. Even for the three forms of early-onset familial ADs caused by mutations in one of three genes (*APP*, *PSEN1*, *PSEN2*), whether it is worth spending money on genetic screening to predict a disease without a cure is still a question. For some patients, this is a choice for them to know more information such as the risk they face of having a child who will later develop AD. For others, they may not want to know something they can not control. Individualizing the preventive strategy for different people is crucial to achieve overall success and to maximize the possibility of reducing the risk of AD and helping those who are suffering from it to have a better life.

5 Summary

AD is an increasing epidemic threatening public health. The etiology of AD has not been fully understood since the disease was identified one century ago. Recent progress in human genetics brings an entry point for us to explore the cause and treatment for AD. Three genes (*APP*, *PSEN1*, and *PSEN2*) have been linked to early-onset familiar AD while *APOE4* has been confirmed to increase the risk of both familiar and sporadic AD. More than a dozen of other genes are

believed to have a potential association with the disease. Although the epidemiology of AD can not be completely explained by genetic factors, the breakthrough in human genomic provides a useful tool for AD prevention. Genetic screening tests have been established and available for persons at high risk of AD. A medical recommendation based on these tests may help these potential patients as well as their families better prepare for a later life with AD.

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阿尔茨海默氏病的流行病学、遗传学及其它

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摘要：阿尔茨海默氏病是一种不断增长的威胁公众健康的流行疾患。男女两性均对此病易感，以女性稍甚。该病患病率在老年人群中呈指数上升，65岁时患病率约1%，至95岁时达到40%-50%。尽管病因尚未被完全了解，遗传因素已被确认在其发病中扮演重要角色。发生在三个基因(*APP*, *PSEN1*, *PSEN2*)中的突变可导致该病，而*APOE4*等位基因与患病的危险增加有关。随着人类基因组研究的进展，可能会有更多与该病相关的基因被发现。目前，应用遗传筛选测试，可以帮助阿尔茨海默氏病的高危人群更好地准备和应对未来可能发生的疾病。

关键词：阿尔茨海默氏病；β- 淀粉样前体蛋白；早老素；载脂蛋白