World-wide distribution of familial Alzheimer's disease

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The familial form of Alzheimer's disease has been recognized in a wide variety of ethnic groups. Additional detailed studies are necessary to document prevalence rates in these groups and to search for the disease in less well-studied geographic areas including Asia and Africa.

ALZHEIMER described the disease that bears his name in 1907. The first well-documented occurrence of Alzheimer's disease (AD) over several generations in a single family was reported by Schottky[1] in 1932. Since that time, evidence has slowly accumulated that there is indeed a genetic form or forms of AD. However, the prevalence of familial AD (FAD) in the general population, the mutation or mutations leading to the disease and the precise phenotypic characteristics of FAD–all are questions remaining to be answered.

The term 'familial' is rather vague and traditionally implies simply more than one case of a condition in a family. The term does not necessarily imply that the disorder is inherited or genetic, since infectious diseases or illnesses resulting from environmental agents can certainly be 'familial'. Epidemiological studies of AD have been quite consistent in demonstrating that approximately 25–30% of index cases with AD have at least one additional relative with dementia[2–4]. Most of these studies are based on evaluation of first-degree relatives. Such findings certainly do not prove that AD is an inherited disease.

The more important question is whether or not AD can be inherited as a single gene Mendelian disorder. The answer is now clearly 'yes', in at least some instances. Many kindreds have been carefully described with pedigree patterns that are overwhelmingly suggestive of autosomal dominant inheritance. That is, there have been multiple generations of affected individuals, males and females are approximately equally affected and there are examples of male-to-male transmission of the disease. Fifty such families were reviewed by Cook *et al.* in 1979 and more than 100 such kindreds are now known to exist[5–11].

It is also possible that there are recessive forms of AD, but these are much more difficult to document. One would expect to find affected siblings who have normal children and normal parents. Such families exist but are difficult to distinguish from the coincidental occurrence of a common nongenetic disease. Also, one might expect increased parental consanguinity in some families with autosomal recessive AD, but this has rarely been discovered.

The neuropathological confirmation of AD at autopsy must also be emphasized because other familial dementing disorders can masquerade as AD, such as Huntington's disease, Pick's disease, Gerstmann–Straussler disease, Creutzfeldt–Jacob disease and some spinocerebellar degenerations[12,13].

AD is often divided into early and late onset groups. This is also true of FAD. An example of well-documented early onset FAD from our genetic investigations is shown in Figure 1, and an example of late onset FAD is shown in Figure 2.

FAD has been reported to occur in families from many countries and a wide variety of ethnic backgrounds. The ethnic backgrounds of the FAD kindreds ascertained in our University of Washington studies are shown in Table 1. These examples generally reflect the diverse ethnic background of the United States. The ethnic background of some of the other large FAD kindreds reported from other institutions is also noted in the table.

It can be seen that FAD has occurred in all countries and nationalities where a careful search has been made. However, there are obviously some large population areas in which autosomal dominant FAD has not yet been identified. These would include Mainland China, India and Black Africa. These apparent deficits are likely to reflect a combination of delayed clinical search for the familial occurrence of AD and low autopsy rates[14].

The demonstration that some forms of early onset FAD are associated with point mutations in the amyloid precursor gene confirms that at least some instances of FAD are inherited as single gene autosomal dominant disorders[15]. However, it is also clear that some FAD kindreds do not carry these APP gene mutations and must represent the presumably autosomal dominant inheritance of some other genetic defect[16].

The prevalence of the autosomal dominant form of

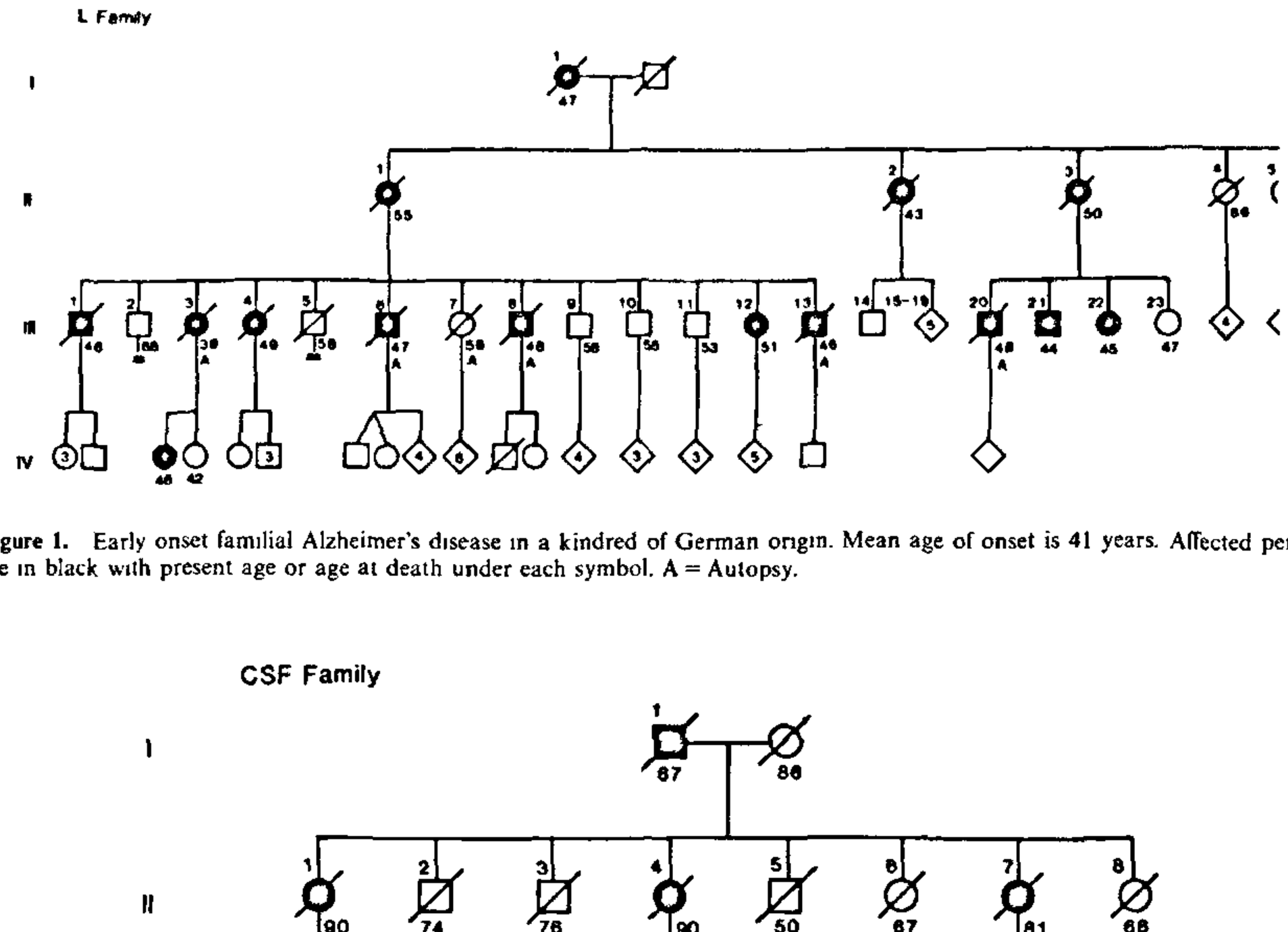

Figure 1. Early onset familial Alzheimer's disease in a kindred of German origin. Mean age of onset is 41 years. Affected persons are in black with present age or age at death under each symbol. A = Autopsy.

Figure 2. Late onset familial AD in a kindred of Danish origin. Mean age of onset is 70 years.

Table 1. Nationality or ethnic background of reported presumed autosomal dominant Alzheimer's disease

1. Belgian	11. Italian
2 Czech	12. Japanese
3. Danish	13. Latvian
4. English	14. Norwegian
5. Estonian	15 Mexican
6. French	16. Russian Jewish
7. French-Canadian	17. Scottish
8. German	18. Spanish
9. Volga German	19. Swedish
10. Irish	

FAD in the general population has never been determined. Large, well-documented, multi-generation kindreds are relatively uncommon, occurring less than 5% of the time in our studies of patients with AD. However, if the penetrance of an FAD gene is low and the expression of the gene may not occur until late in life, the actual occurrence of FAD may be greatly underestimated[17,18]. Whether there are ethnic differences in the prevalence of a gene or genes for FAD will take many years to determine. It is noted that the rare FAD mutation in the APP gene has occurred in both Caucasians and Japanese, suggesting that the mutation rate is at least not as low as in some other autosomal dominant brain disorders such as Huntington's disease[19].

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Principles of linkage analysis applied to genetic mapping of familial Alzheimer's disease

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Linkage analysis of Alzheimer's disease is technically very demanding because of the tremendous amount of missing data inherent in such a late-onset disease. However, given careful attention to the basic principles which underly the use of the analysis techniques, it should be possible to map genes responsible for the disease. Genetic heterogeneity, difficulties in determining penetrance functions, and difficulties in performing the computations are all complications in the analysis, but these issues should not be used as license to make decisions which violate assumptions behind the basic methods used.

Introduction

ALZHEIMER'S disease (AD) is the most common form of dementia in the elderly, claiming as victims as many as a quarter of individuals who live into or beyond their eighties[1]. A genetic component to this disease is strongly suggested by a number of studies[2–5], and is supported by the existence of a number of pedigrees with early onset disease in which approximately half the family members are affected in multiple generations (reviewed by Bird, this issue), as is expected for a dominant disorder. Because of this evidence, several groups have taken up the challenge trying to map, and eventually identify, the gene(s) responsible for this disease.

AD poses many challenges in the use of statistical techniques to map genes contributing to the disease. As a result, these studies are much more difficult for AD than for most Mendelian genetic diseases, and have led to controversies in the interpretations of the results of linkage studies, for example, with markers near the centromere on chromosome 21 (refs. 6–10). One explanation of the results is that there is genetic heterogeneity for the disease[7,11]. While there is now excellent evidence that there are several different mutations in the same codon in the amyloid precursor protein (APP) on chromosome 21 which cause AD[12,13], only a small handful of families so far studied has had these mutations. No sporadic cases have been found with these mutations, indicating that they are not responsible for the majority of AD in the populations so far studied, including much of the early onset familial AD[14]. As efforts continue to identify other genes responsible for this disease, similar controversial results are likely to occur; for example, suggestive reports of linkage to chromosome 19 have been