Clinical rationale of genetic testing in dementia

The genetic component of some cases of dementia has long been recognised. In 1987 a locus on chromosome 21 was found to be associated with a very aggressive form of Alzheimer’s disease with a strong familial transmission (autosomal dominant inheritance). Four years later the defect was identified in a point mutation of the amyloid precursor protein encoding gene. Members of families carrying the mutation always developed Alzheimer’s disease by about 65 years of age, and members not carrying the mutation did not. The very high penetrance of the mutated trait pointed to amyloid as the potential causative agent of the disease and suggested the potential use of searching for this mutation in the diagnostic clinical setting. In subsequent years, the search for other cases of dementia with a genetic component was disappointing. The genetics of some familial dementias were described. These dementias included familial prion diseases, hereditary cerebral haemorrhages with amyloidosis, Dutch type, chromosome 17 and chromosome 3 linked forms of frontotemporal dementia, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The genetic defect of Huntington’s disease was localised on chromosome 4, and some more pathogenic amyloid precursor protein mutations were discovered, usually with very high penetrance. However, the low frequency of these cases in the overall demented population led clinicians working on dementia to consider the genetic component to be of little practical relevance. The discovery in 1993 of the association between the highly prevalent late onset form of Alzheimer’s disease and the ɛ4 allele of the apolipoprotein E gene (APOE) and in 1995 between some families with autosomal dominant Alzheimer’s disease and presenilin-1 (PS1) and presenilin-2 (PS2) mutated genes on chromosomes 14 and 1 kindled new interest. Diagnostic kits for APOE genotyping are now commercially available, the presenilin genes have been fully sequenced, the proteins synthesised, and clues to their physiological action are increasingly being discovered. However, the usefulness of these new discoveries in daily clinical practice is often unclear and deserves critical discussion.

This review considers the genetic issues related to Alzheimer’s disease as these are the most prevalent in clinical practice, have the largest body of literature, and are those with the most recent and promising developments. Guidelines on genetic testing in Huntington’s disease are well established and can be found elsewhere. It is emphasised that the conclusions of this paper should be treated with caution due to the rapid evolution of this field of medicine.

Genetic pathogenic mutations and genetic risk factors: biology and epidemiology

Genetic studies in dementia are relevant to the understanding of the pathogenesis of the disease, and as clinical tools for diagnosis and prognosis. To understand the theoretical and practical implications of such studies, a brief introduction on amyloid precursor protein, presenilin mutations, and genetic risk factors may be useful.

Mutations of amyloid precursor protein have a very high penetrance, nearly 100% and PS1 mutations are similar, suggesting that the encoded proteins might be very close to the core of the biochemical trigger starting the cascade that leads to neuronal degeneration and death. Presenilins might cause Alzheimer’s disease by increasing amyloid deposition in the brain, further underlining the central role of amyloid in the pathogenesis of Alzheimer’s disease. More indirect evidence points to an effect on tangle formation.

The search for mutated genes in autosomal dominant Alzheimer’s disease has a theoretical basis in the one gene, one disease model, assuming that the Alzheimer’s disease “trait” comprises several subtraits, each influenced by a single gene. It is likely that mutations of amyloid precursor protein, PS1, and PS2 genes are responsible for a very large proportion of all cases of autosomal dominant Alzheimer’s disease, amyloid precursor protein accounting for 2%-3%, PS1 for about 50%-80%, and PS2 mutations for the remaining 15%-20% (Volga-German kindred). However, autosomal dominant Alzheimer’s disease is very rare in practice. What is not rare (at least 25% of all cases of Alzheimer’s disease) is a history of dementia in one first degree relative. This criterion is much less stringent than those underlying autosomal dominant inheritance and defines what is often referred to as “familial Alzheimer’s disease”. Unfortunately, this term has also been given to some kindreds with autosomal dominant Alzheimer’s disease. That there is a basic difference between autosomal dominant Alzheimer’s disease and familial Alzheimer’s disease is supported by the finding that in clinical series in which familial Alzheimer’s disease is frequent but autosomal dominant Alzheimer’s disease is rare, the frequencies of amyloid precursor protein, PS1, and PS2 mutations are low.
The search for genetic or environmental risk factors in dementia and Alzheimer’s disease has a long history.46 The discovery of the association of the ε4 allele of APOE with Alzheimer’s disease rightly kindled great interest as for the first time a highly prevalent and easily detectable factor was consistently found related to the disease. Apolipoprotein E is a lipoprotein carrying cholesterol in the blood, and is the only apolipoprotein produced in the brain, where it has a role in damage repair.45 The APOE gene has three common allelic forms, ε2, ε3, and ε4, with different frequencies (around 5%-10%, 75%-85%, and 10%-15% in white populations),46 coding for the E2, E3, and E4 protein isoforms. Corder et al.53 reported a close association between the ε4 allele of APOE and late onset familial Alzheimer’s disease. Members of these families carrying two (ε2/ε4) or one (ε4/-) copy of the ε4 allele were overrepresented and ε4/ε4 family members developed Alzheimer’s disease more often (91% v 47% and 20%) and earlier (at age 68 v 76 and 84 years) than ε4/- and non-ε4 carriers respectively. Cross sectional studies later confirmed the higher frequency of the ε4 allele in the more prevalent late onset sporadic form.16 This finding has been consistently replicated throughout the world, with very rare exceptions.48-50 However, it has become increasingly clear that a relevant proportion of healthy ε4/ε4 elderly people never develop Alzheimer’s disease, and that a relevant proportion of patients with Alzheimer’s disease are not ε4 carriers.51-55 These findings indicate that the ε4 allele has a quantitative trait (involving probabilistic propensities) rather than a one gene, one disease (involving deterministic programming) effect, implying that the Alzheimer’s phenotype can be expressed due to the converging effects of the ε4 allele with other genetic or environmental factors. As a consequence, its biology and clinical application must be distinct from those of the pathogenic mutations. The biological role of apolipoprotein E in Alzheimer’s disease is still unclear. At least three hypotheses have been proposed. It was originally shown that apolipoprotein E might enhance β-amyloid deposition in the brain by binding with high avidity.56 Alternatively, the E3 isoform might exert a protective effect by slowing phosphorylation of τ protein and delaying tangle formation.57 Others think that the role of apolipoprotein E in Alzheimer’s disease might be due to its physiological effect as a lipid carrier in the brain. The E3 isoform has been shown to cause enhanced and the E4 isoform reduced neurite growth in vitro studies.58 This idea is also supported by findings that the ε4 allele is a risk factor for incident vascular dementia and poor recovery after head trauma.59

Recently, an allelic association similar to that of APOE has been reported for a polymorphism (alleles 1 and 2) in the non-transcribed part of the PS1 gene in a clinical series of 208 patients with Alzheimer’s disease,60 with homozygosity of the allele 1 of PS1 being responsible for 22% of cases. Similarly, an allelic association of the very low density lipoprotein receptor gene with sporadic Alzheimer’s disease has been reported in Japanese patients61 and another association with the α1-antichymotrypsin gene in white62 patients. However, attempts to replicate these findings have given conflicting results.63-68

Clinical genetic testing

The use of genetic testing for pathogenic mutations and APOE might be envisaged in a clinical setting—at an individual level—or in an epidemiological setting—at a population level.

GENETIC TESTING AT AN INDIVIDUAL LEVEL

At the individual level genetic testing in the cognitively impaired patient can be used to increase diagnostic accuracy and detect transmissibility. In the as yet cognitively unimpaired subject it can be used to predict disease development and age of onset. The questions arising in autosomal dominant, familial, and sporadic cases are different and require separate discussion.

Autosomal dominant Alzheimer’s disease

Less than 200 kindred with a clearly autosomal dominant form of Alzheimer’s disease have been reported.46 In dementia research, case ascertainment in pedigrees is more difficult with greater variation in age at onset of the disease in different family members and with older age at onset.70-72 However, transmissibility of the disease in these families is often clear. The most relevant issue is the prediction of development of disease in the cognitively unimpaired relatives of a proband. Although data on PS1 and PS2 mutation penetrance are still scarce, it is likely that the detection of one of the known amyloid precursor proteins, PS1, or PS2 mutations in an unaffected relative is associated with a probability of developing the disease close to 100%. However, unaffected relatives are interested to know not only whether they will develop the disease, but also when. Amyloid precursor protein mutations have 100% penetrance within 2-5 SD from the mean age of onset for the family.73 The range of age of onset of Alzheimer’s disease associated with mutations of the amyloid precursor protein, PS1, and PS2 genes is very wide if all families are pooled together (40 to 65, 30 to 65, and 40 to 90 respectively).74 The amount of within family variation of age of onset of the same mutated gene is narrower, at least in PS1 families (about 12±6 years in PS2 families).75 However, the range is sufficiently wide in most families to generate great uncertainty on the predictability of age of onset in mutation carriers.18 74 77 Furthermore, these findings indicate that environmental or other genetic factors have a powerful modulatory effect on the genetic defect. The APOE genotype might be one such factor, in that the ε4 allele has been shown to reduce the age of onset in families with amyloid precursor protein mutations;63 however, the ε4 allele does not have any effect in families with PS1 mutations.69-71

The prediction of age at onset by genetic markers is not unique to autosomal dominant Alzheimer’s disease; it occurs also in the case of CAG triplet repeats and Huntington’s disease. Determination of the CAG triplet can accurately and usefully predict whether a subject at risk will develop Huntington’s disease.77 It is also known that age of onset of Huntington’s disease is related to the number of CAG repeats, a higher number of repeats being associated with younger onset.78 However, its 95% confidence interval for any given number of CAG repeats is over 50 years.79 In this case, a genetic factor is responsible for some of the clinical variability, but the contribution is too little to be practically useful. This emphasizes the fact that the usefulness of genetic testing in clinical dementia critically depends on the amount of clinical variability accounted for by genetic factors.80

Although occasionally the detection of pathogenic mutations can be usefully employed for genetic counselling,81 the overall very low prevalence of genetic defects in Alzheimer’s disease militates against indiscriminate screening for amyloid precursor protein, PS1, and PS2 mutations in clinical practice. Screening for genetic mutations in specific subpopulations (for example, patients with early onset dementia and very positive family history) might prove cost effective as it would increase the ratio of those with a positive test to those with a negative test.
Guidelines on when and how to perform predictive genetic testing in autosomal dominant Alzheimer’s disease had been provided before the PS1 and PS2 genes had been identified, but updated guidelines taking the new findings on presenilins into account are lacking.

Familial Alzheimer’s disease

About 300 familial cases with early onset taken from clinical series have been screened for PS1 and 200 for PS2 mutations. No PS2 mutations have been found, and PS1 mutations occurred in 5% of cases. The prevalence of these mutations in sporadic early onset cases is similar, whereas in the familial late onset cases it is lower. Therefore, the usefulness of a routine search for the known mutations in patients with familial Alzheimer’s disease seems limited.

Having a family history of Alzheimer’s disease on the other hand, does seem to increase the risk of developing the disease, which points to the effect of a genetic factor. Although the genetic factor responsible for this increased susceptibility has not yet been identified, it has been suggested that APOE might account for the familial aggregation. This view is supported by the finding that family history for dementia is more often reported by Alzheimer’s disease e4 carriers than non-e4 carriers.

Sporadic Alzheimer’s disease

The e4 allele is more common in patients with sporadic late onset Alzheimer’s disease than in elderly controls (about 40% v 10%-15%). This finding, together with the increased frequency of the e4 allele in familial late onset Alzheimer’s disease, suggests that the detection of an e4 allele in a demented patient might increase the likelihood of the patient having Alzheimer’s disease. APOE genotyping has been thought to increase the accuracy of diagnosis of Alzheimer’s disease. It has been argued that detection of an e4 allele in a demented patient confers a 95% probability of Alzheimer’s disease. However, this is true only if the frequency of the e4 allele in the non-Alzheimer’s disease dementias is not increased. Some authors have reported increased e4 allele frequency in Lewy body dementias and vascular dementias. If this is the case, the role of APOE genotyping in the diagnosis of Alzheimer’s disease might be less important than previously claimed, and the value of testing might be debated.

The most recent guidelines on the use of APOE genotyping in dementia cautiously accept the possibility that APOE genotyping might be a useful confirmatory diagnostic test, but do not recommend its use until fully epidemiological data are available. Recently, Saunders et al have shown in a series of 67 necropsied cases of probable Alzheimer's disease (57 with Alzheimer's disease confirmed by necropsy and 10 other dementias) that all the 43 e4 carriers had Alzheimer’s disease confirmed at necropsy (100% predictivity). This suggests that APOE genotyping, when restricted to those demented patients clinically diagnosed as probable Alzheimer’s disease, might provide a definite diagnosis in about two thirds of cases.

The clinical meaning of APOE genotyping as a predictor of development of disease is less clear. It has been shown with PET that elderly non-demented e4/e4 subjects and relatives of patients with Alzheimer’s disease carrying the e4 allele have cerebral metabolic defects similar to those of patients with Alzheimer’s disease. Furthermore, non-demented elderly e4 carriers have 2-2 to 3-7-fold greater risk of developing Alzheimer’s disease. These findings contrast with those obtained from cross sectional clinical series indicating a much closer association of the e4 allele with having Alzheimer’s disease (risk of 6-2, 95% confidence interval 4-9 to 7-8 in a large series of combined studies). This means that the high frequency of the e4 allele in Alzheimer’s disease is only partly due to the increased risk given by the e4 allele. The remainder might be due to an enrichment of e4 in the Alzheimer’s disease population due to longer duration of disease in Alzheimer’s disease e4 allele carriers, or to impoverishment of the e4 allele in the non-Alzheimer’s elderly population due to selective cardiovascular mortality in e4 allele carriers, or both.

It must be emphasised that currently available guidelines strongly advise against APOE genotyping aimed at disease prediction in asymptomatic subjects.

GENETIC TESTING AT THE POPULATION LEVEL

Genetic testing at the population level is aimed at selecting large groups of at risk or affected people for primary or secondary prophylaxis. Whatever estimate of the strength of the association between the e4 allele and Alzheimer’s disease is accepted, the magnitude of the APOE associated risk for Alzheimer’s disease is epidemiologically significant. It has been claimed that about 10% to 40% of all cases of Alzheimer’s disease are due to the effect of the e4 allele. However, such a proportion of cases might be spared if the risk factor should be eliminated. This has relevant implications for public health, and research into the therapeutic issues of APOE continues.

Alzheimer’s disease e4 carriers might be differentially responsive to therapy with cognitive enhancers and the biology of the E4 isoform in the brain is being investigated with the aim of finding drugs that might counteract its effects. It seems likely that sometime in the future APOE genotyping might be used in screening programmes to select asymptomatic e4 carriers for primary prophylaxis or to increase the sensitivity of epidemiological case finding tools aimed at detecting early Alzheimer’s disease for secondary prophylaxis.

The clinical applications of genetic testing in dementia are still in their preliminary stages. The search for the known defects can be useful in a limited number of cases, but prediction of age of onset in mutation carriers, even when positive, is fraught with great uncertainty. The e4 allele of APOE is an established risk factor for Alzheimer’s disease, accounting for 10%-40% of all the cases, but its usefulness as a diagnostic test for Alzheimer’s disease must be confirmed, and its role as a screening tool in populations must be assessed in future studies. There is also a need to compute reliable estimates of the age specific risk for Alzheimer’s disease associated with the e3/e4 and e4/e4 genotypes. To be clinically useful, genetic research work in dementia will need to shift from the one gene, one disease theory towards the quantitative trait model to provide estimates of the amount of clinical variability that can be accounted for by genetic factors.

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NEUROLOGICAL STAMP

Julius Wagner-Jauregg (1857–1940)

The Austrian neuropsychiatrist Julius Wagner-Jauregg was born in Wels in 1857. He studied medicine in Vienna, where he earned his “venia legendi”, an advanced doctoral degree required for university lecturers, in 1885. He spent four years at the University Clinic in Graz before becoming head of the Viennese Department of Psychiatry, a position he held from 1893 to 1928. His intensive study of cetrinism served as a basis for his specialisation in the problems of goitre. In 1887 he published a paper on the influence of feverish illnesses on psychoses, and 30 years later, during the first world war, introduced the use of tetrabenazine (Plasmodium vivax) infection in the treatment of late symptomatic neurosyphilis. He was awarded the Nobel prize in 1927 for discovering the therapeutic value of this “malaria vaccination” in the treatment of progressive paralysis. Julius Wagner-Jauregg died in Vienna on 7 September 1940. Austria issued a commemorative stamp in honour of the 100th anniversary of the Nobel prizewinner’s birth.

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