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Genetics Of Alzheimer's Disease: Just How Is Molecular Biology Going To Help Grandma?

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Revolutions are sometimes silent and at other times over-rated. It is the privilege of historians to discern patterns and pronounce upon the significance of new ideas or actions. However, the pace of scientific advance demands an occasional pause for review; particularly for Alzheimer's Disease (AD) which in the space of two decades has emerged from being an obscure, rarely applied diagnosis to being a major cause of death in the United States and other developed nations. Research into AD has also become a tremendous scientific endeavour: output has increased from an average of 3 papers per year in the 1960's to over 2,400 papers in 1995 alone. There are interesting sociological, political as well as scientific reasons for this transformation[1] which bear relating.

Dementia is an ancient syndrome written about by Roman physicians a thousand years ago and noted to occur in old age by no less an observer than Shakespeare. However, it was only in the 19th century that physicians formalised the notion of old age being a medical problem due to inevitable organic alterations, thus giving rise to the concept of "senile dementia". In 1906, Alzheimer used newly developed neuropathological staining techniques to describe plaques and tangles in a middle aged female with dementia and prominent behavioural problems. In doing so, he established a conceptual distinction between senile dementia (symptoms occurring after the age of 65) which was a consequence of ageing and pre-senile forms of dementia (symptoms occurring between 40 and 65) which had characteristic neuropathological features. Later workers attributed senile dementia to arteriosclerosis and relegated AD into being a rare form of pre-senile dementia. Little progress was made since the study of dementia was distinctly unfashionable and few tools or resources were available.

Nevertheless, by the mid 1970s, studies had shown that many cases of senile dementia could not be distinguished clinically, neuropathologically or ultrastructurally from pre-senile cases of AD and it was proposed that the age distinction be abandoned[2]. Furthermore, simple projections from epidemiological studies suggested that with an ageing population, the incidence and prevalence of AD would rise to become a major health challenge. The magnitude of the problem and growing public support provided the impetus for more generous funding of research which in turn has led to a number of remarkable advances in understanding the pathogenesis of AD. In particular, there has been the recent discovery of several genes in which mutations lead to early onset familial Alzheimer's Disease (FAD), as well as genetic risk factors for developing late onset familial and sporadic AD. These genetic findings have turned the clock back by once again raising the issue of an age distinction in AD. Such is the fate of scientific ideas!

It should be clarified that only a minority, no more than 15%, of AD patients have FAD. Most have an early onset of symptoms but there are a few families where the onset is late. However, the large majority of AD patients are sporadic. Two main strategies are employed by geneticists in hunting down genes responsible for disease. Firstly, linkage studies can locate the chromosome on which disease genes reside, whereupon genes in that particular locus can be individually screened. Secondly, candidate genes which produce proteins thought to be involved in the disease can be analysed for mutations. Either approach requires a great deal of hard work and good fortune to succeed.

The first AD gene to be discovered was the amyloid precursor protein (APP) gene on chromosome 21 which had already been linked to early onset FAD in family studies and by the association of Trisomy 21 (Down's Syndrome) with AD pathology. As indicated by its name, APP can be metabolised into the βA4 amyloidogenic protein which forms the senile plaque. In 1991, it was reported that autosomal dominant mutations in the APP gene was the molecular basis of AD in some families[3]. However, it soon became apparent that only a small number of FAD cases could be accounted for by such mutations.

The next breakthrough came as a result of dedicated molecular epidemiology, persistence and serendipity. The careful study of late onset FAD families had come to the controversial conclusion that the gene involved was on chromosome 19. βA4 was used as a molecular "hook" to identify suitable candidate genes for testing. One such protein which bound avidly to βA4 was apolipoprotein E (APOE) which was recognised as a potential candidate because it was also located in the correct chromosomal locus. It was then demonstrated and confirmed by many other groups that inheritance of the ε4 allele of the APOE gene is associated with both late onset FAD[4] as well as sporadic AD[5]. It must be emphasised that the APOE ε4 allele is a risk factor rather than a causative gene.

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Linkage studies had previously shown that the majority of early onset FAD cases were due to a genetic defect on chromosome 14. It took an immense effort from several groups to finally locate the gene (presenilin 1) which turned out to code for a protein which was novel and had no known function in humans[6]. Armed with the presenilin 1 gene sequence, it did not take scientists very long to identify a closely related gene (presenilin 2) responsible for early onset FAD localised to chromosome 1[7].

How does all this exciting science help the clinician? Unfortunately, no diagnostic test is as yet available for the majority of patients with sporadic AD, although APOE has been proposed to be of help in the differential diagnosis of dementia[8]. Development of tests for early pre-clinical dementia such as imaging techniques (MRI, fMRI and PET)[9]. CSF neurochemistry (for tau and βA4)[10] and neuropsychometry may be facilitated by genetic ascertainment of at risk cases in FAD. However, there are ethical problems given that no effective treatment exists. The greatest promise lies in understanding how these genetic factors affect the pathophysiology of AD; the hope being that any insights may lead to therapeutic targets and modifiable riak factors being identified.

Exciting as these advances are, the triumph of molecular biology is still awaited. Meanwhile grandma (and grandpa) will still have to depend on having a sensible loving family, nurses and physicians to care for them.

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