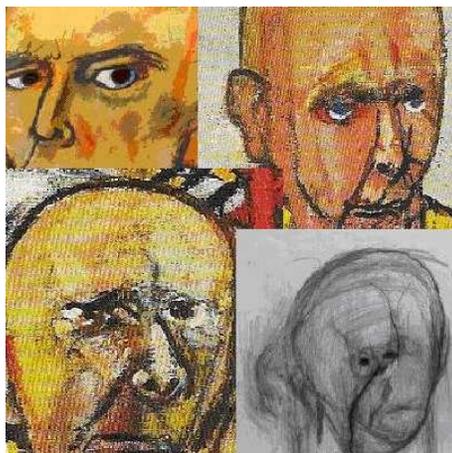


Tangled

Vivienne Baillie Gerritsen

Dementia is a debilitating experience. For the afflicted, and for those who are close to them. Alzheimer's disease (AD) is a form of dementia from which millions of people suffer worldwide. Besides the well-known symptom of memory decline, people with Alzheimer's are progressively troubled by language impediments and peculiar visuospatial perception, for example, but also behavioural and psychiatric dysfunctions. Though the passing of the years is the main cause for what is known as sporadic AD, there is also a far more rare hereditary form. Rare or not, both types of AD are the result of irreversible neuron loss, brought on by protein deposits in the central nervous system. Detecting Alzheimer's is not a trivial affair. The first symptoms are not different from the normal process of aging. And it takes years before serious handicaps emerge. However, there seems to be one protein – known as apoE4 – whose presence is proving to be a sure indicator of whether or not someone is prone to AD.



Four self-portraits by the American artist William Utermohlen (born 1933) afflicted with Alzheimer's, and painted between 1996 and 2000.

©2006 Galerie Beckel-Odille-Boicos, Paris

Alois Alzheimer described the clinical and neuropathological traits of Alzheimer's disease in November 1906, at the 37th meeting of the Society of Southwest German Psychiatrists. Five years earlier, Alzheimer had admitted a middle-aged woman into the Frankfurt hospital, who was suffering from memory loss, focal symptoms, delusions and hallucinations. She died in April 1906 and Alzheimer sent her brain to Munich where the novel technique of silver-staining highlighted the accumulation of protein

plaques and tangles. Such deposits are still used today to define the neuropathological characteristics of the disease – although they are now known not to be particular to AD.

The accumulation of neuritic plaques and neurofibrillary tangles in our brain is a natural consequence of the passing of the years. However, in most cases, their accumulation is minimal and does not hinder normal neuronal function. The proteins at the heart of these plaques and tangles are amyloid- β and tau, respectively. In healthy organisms, both are soluble proteins. In hereditary AD, genes that are directly involved in the formation of these plaques and tangles are passed down through generations. Though sporadic AD – the form of AD that hits the great majority of those afflicted – presents the same neurophysiological traits, it is still not known what causes them. Why do some develop AD while others do not? ApoE could be an answer. Though just a whispered one.

Accompanied by hordes of other apolipoproteins, ApoE's first function is to transport lipids, usually by cell-mediated endocytosis via an apoE receptor – of which there are many kinds. ApoE is thought to have variable structural conformations, depending not only on the size and shape of the lipids it binds but also on its receptor. The N-terminus docks to the apoE receptor while the C-terminus binds the lipid. Once a lipid is bound, the initial

loose 3D structure of apoE is believed to adopt a hairpin conformation and then a belt-like configuration around a discoidal bilayer of phospholipids. Besides lipid transport, apoE seems to be involved in a number of other processes such as apoE fragmentation into toxic products, membrane disruption, neuronal sensitivity to injury and recovery. It is further known to have antioxidant properties and is associated with amyloid β -peptide and plaque formation.

All these mechanisms are the fruit of three common apoE isoforms: apoE2, apoE3 and apoE4. And where multiple functions are involved, rests a hive for multiple diseases. Indeed, together, the apoE isoforms affect the clinical outcome of a host of cardiovascular, neurodegenerative, and viral infectious diseases, including atherosclerosis, Alzheimer's disease, hepatitis C and HIV. Each isoform structure behaves differently. For instance, apoE4 forms partially unfolded structures far more readily than its peers. Such a conformation not only facilitates lipid-binding but also makes apoE4 more sensitive to proteolysis. What is more, apoE4 is the apoE isoform which – when present – is proving to be an indicator of AD, or a sign of AD predisposition. How apoE4 is

involved in AD remains a mystery but this particular allele does seem to have a role in neuronal plasticity and arborisation, as well as amyloid- β accumulation – traits which have a direct effect on the process of memory for instance.

No one gene will prove to be the definite Alzheimer gene. Besides the simple passing of time, AD is the result of a variety of genetic and environmental instances. To date, existing therapies relieve symptoms such as depression or insomnia, but there is still nothing that can halt – or even slow down – the process of neuron loss. Researchers seem to have put their finger on a probable genetic indicator – apoE4 – although almost half of the AD population does not carry the apoE4 allele... Concentrating their efforts on apoE4's structure and biochemistry will surely lead to a greater understanding of its function, and in so doing perhaps give a way of challenging Alzheimer's ugly face. Such an ugly face, that James Watson – the American component of the discovery of the helical structure of DNA – who has had his genome sequenced, announced that he didn't wish to know whether he was the owner of the apoE4 isoform or not.

Cross-references to Swiss-Prot

Apolipoprotein E precursor, *Homo sapiens* (Human) : P02649

References

1. Goedert M., Spillantini M.G.
A century of Alzheimer's disease
Science 314:777-781(2006)
PMID: 17082447
2. Hatters D.M., Peters-Libeu C.A., Weisgraber K.H.
Apolipoprotein E structure: insights into function
Trends Biochem. Sci. 31:445-454(2006)
PMID: 16820298
3. Hill J.M., Bhattacharjee P.S., Neumann D.M.
Apolipoprotein E alleles can contribute to the pathogenesis of numerous clinical conditions including HSV-1 corneal disease
Exp. Eye Res. 84:801-811(2007)
PMID: 17007837