

normal to incipient LOAD — an early phase of Alzheimer's disease. These data indicate that the *APOE4* status of an individual reflects a prodromal, or 'primed', state for developing LOAD.

Notably, transcriptional changes observed during normal ageing (through comparison of those under 75 years of age with those over 85) overlapped significantly with LOAD, but not with changes specific to *APOE4* carriers. That certain transcriptional alterations in LOAD are seen either with ageing or with *APOE4* status suggests that the contributions of *APOE4* to LOAD are mechanistically distinct from those of ageing. A potential caveat of this analysis, however, is the use of a hard categorical cut-off of age 75, rather than, for example, 65 — the age below which Alzheimer's disease is considered early onset. In this regard, a non-categorical quantitative analysis of transcripts associated with ageing should provide maximum analytical power.

Network-level co-expression analyses have been used successfully before to investigate disease-related molecular pathways in various neuropsychiatric^{5,6} and neurodegenerative disorders, including Alzheimer's disease^{3,7}; such analyses permit an unbiased, systems-level understanding of disease mechanism. Rhinn and colleagues' work differs from other network-based co-expression approaches in focusing on differential co-expression — that is, on changes in co-expression patterns observed between control and disease samples. The authors, who used a transcriptome-wide network-analysis tool called differential co-expression correlation analysis (DCA), provide extensive experimental support for the targets identified, which adds an unprecedented level of validation.

Of the 215 differentially expressed genes Rhinn *et al.* found by comparing *APOE4* carriers and non-carriers, 20 are top candidate 'network node' genes on the basis of their DCA ranking. Many of the node genes had been previously implicated in regulating amyloid precursor protein (APP) processing and intracellular sorting⁸, supporting their relevance.

The authors performed various *in vitro* experiments to validate several of the node genes, in particular *SV2A* and *RNF219*. In cell lines and in human induced neurons, obtained by the process of cellular reprogramming, they show that *SV2A* affects APP processing through the regulation of endocytosis and intracellular trafficking. They also find that *RNF219*, which had not been previously associated with APP processing or Alzheimer's disease, acts as a nuclear regulatory mediator of *APOE4*-induced APP endocytosis and its processing by the β -secretase enzyme.

The researchers muster and analyse multiple independent data sets, including published GWAS, which provide further support for the key role of the DCA hits in *APOE4*-mediated susceptibility to Alzheimer's disease, and make a case for further testing and replication studies

using this gene set. For example, they show that, together with the *APOE4* status, common genetic variants of *RNF219* and *FYN* — another node gene with a role in endocytosis — are correlated with age of LOAD onset. Indeed, using publicly available human positron-emission tomography imaging data from the Alzheimer's Disease Neuroimaging Initiative, Rhinn *et al.* find that variations in *RNF219* significantly affect APP processing in *APOE4*-negative healthy individuals — consistent with a prodromal role of this, and possibly other, A/E genes.

Overall, the present paper significantly advances our knowledge of molecular and genetic mechanisms that modify LOAD risk, further implicating defects in endocytosis and intracellular trafficking in Alzheimer's disease development^{9,10}. The identification of key regulatory molecules and pathways involved in *APOE*-based risk for LOAD sets the stage for investigating their link to other deficits in this disorder, including immune function and metabolism of hyperphosphorylated tau protein, which forms the disease's characteristic neurofibrillary tangles. Ultimately, such investigations should lead to molecularly targeted therapeutics.

By demonstrating distinct mechanisms that depend on *APOE* status in LOAD, another implication of this work is that different genetic forms or subtypes of Alzheimer's disease may have specific underlying mechanisms and respond differently to treatment. If so, as with cancer, therapies based on genetic and genomic diagnostics may be most effective.

This work is also exemplary in demonstrating the extraordinary value of publicly available data resources. Published data on human gene expression, Alzheimer's disease GWAS and neuroimaging provide the pillars of Rhinn and collaborators' paper. Integrative analyses of these data by the authors, and previously by others^{3,7}, weaken the view that substantive biological experimentation only takes place at the wet bench, and highlight the value of innovative re-analyses of existing data⁶. ■

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50 Years Ago

'The Delhi Pillar' — The mystery which has enveloped this quite remarkable piece of metal should be once and for all removed as a result of three papers published in the ... *Journal of the National Metallurgical Laboratory of India* ... All that has been previously written is summarized and the theories propounded to explain its resistance to corrosion are collected ... Made by hammer-welding small balls of native iron ... its resistance to corrosion during the 1,600 years or so of its existence is ascribed to the combined influence of a number of normal, favourable factors. Among these are included the climate and freedom from pollution of the atmosphere. Secondly, to a progressively decreasing rate of attack due to the building up of a protective layer of oxide and scale during the early years of exposure. That in the past on ceremonial occasions the pillar was anointed appears to be probable ... This is supported by the X-ray analysis of a minute sample of the surface coating ... which contained no iron and only quartz and chalk providing another source of protection.

From *Nature* 3 August 1963

100 Years Ago

We have applied the new methods of investigation involving the use of X-rays to the case of the diamond, and have arrived at a result which seems of considerable interest. The structure is extremely simple. Every carbon atom has four neighbours at equal distances from it, and in directions symmetrically related to each other. The directions are perpendicular to the four cleavage or (111) planes of the diamond; parallel, therefore, to the four lines which join the centre of a given regular tetrahedron to the four corners. **W. H. Bragg & W. L. Bragg**
From *Nature* 31 July 1913