Published in final edited form as:

JAMA Neurol. 2016 April ; 73(4): 383–384. doi:10.1001/jamaneurol.2015.4984.

To dement or not to dement, that is the question

Bryan J. Traynor, M.D., Ph.D.^{1,2} and Yevgeniya A. Abramzon^{1,3}

¹Neuromuscular Diseases Research Section, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA

²Department of Neurology, Brain Sciences Institute, Johns Hopkins University, Baltimore, MD 21287, USA

³UCL Institute of Neurology and MRC Centre for Neuromuscular Disease, Queen Square, London WC1N 3BG, UK

Up until a decade ago, amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) were considered to be distinct neurodegenerative conditions, one clinically characterized by paralysis, the other by cognitive dysfunction. Epidemiological, clinical and neuropathological data now make it clear that the two conditions form a spectrum of disease.^{1,2} Genetic studies have played a central role in teasing apart the cellular mechanisms underlying this overlap. In particular, the pathogenic repeat expansion in the *C9orf72* gene was found to account for a large percentage of ALS-FTD cases.^{3,4}

Despite these advances, the relationship between ALS and dementia is only partially resolved. A particularly vexing problem is that we do not understand why some ALS patients develop dementia, whereas others do not, even when the patients are close family relatives carrying exactly the same mutation. Environment and lifestyle factors almost certainly play a role in determining this outcome. Nevertheless, efforts have largely focused on identifying the genetic factors that drives a patient toward dementia, in part because modern genomic technologies allow these hypotheses to be relatively easily tested.

Genetic variants that determine whether an individual carrying the *C9orf72* repeat expansion will present with ALS or FTD have already been reported. For example homozygosity for the minor allele of rs3173615 in *TMEM106B* protects carriers of the repeat expansion from developing FTD, but not from developing ALS.⁵ These studies largely focus on predicting whether the initial presenting features would be muscle paralysis or frontal lobe dysfunction.

In contrast, Chiò and colleagues followed a cohort of ALS patients over time to identify cases that developed dementia over the course of their illness and those who did not.⁶ Using this information, they then tested whether *APOE* genotype influenced this outcome. They found that the presence of an *APOE* ϵ 2 allele increased the risk of FTD by nearly three fold.⁶ This is not the first time that *APOE* has been studied in ALS patients. Previous studies, however, focused on whether this allele increased risk of developing ALS or altered the age of onset, and were either negative or unconvincing.^{7–9} The innovative feature of Chiò *et al* is

that they evaluated *APOE*'s effect on longitudinal outcome, not just presentation.⁶ This is a subtle but crucially important distinction, as their results show.

The most obvious strength of the Chiò *et al* study lies in their use of a population-based, longitudinal registry of ALS without which they would not have been able to evaluate the long-term cognitive status of their patients. This Northern Italian registry has been in existence for fifteen years¹⁰, and their report beautifully illustrates how such large-scale data collection efforts can be leveraged to answer important questions in the field.

The recognition of *APOE* as a risk factor for dementia in ALS has immediate implications for clinical care of patients. Knowing that an individual is likely to dement will help prioritize the establishment of a living will at a time when the patient is still able to participate, and will help caregivers cope with the behavioural changes arising from the illness. It will also facilitate genetic counseling of other family members.

In addition, the identification of *APOE*'s role has broader implications for how we think about and perceive neurodegeneration. As neurologists, we are trained to diagnose patients according to their presenting symptoms. This paradigm retains obvious clinical utility, but it is increasingly recognized that neurodegeneration does not respect these silos and is more dynamic in nature. Pathologists frequently observe multiple types of inclusions in autopsy brains¹¹, and geneticists are increasingly reporting that mutations in a gene that causes one form of neurodegeneration increase risk in other forms of neurodegeneration.^{12,13}

The current study is certainly a good step forward in our understanding of the genetic architecture underlying ALS and dementia. But like all good science, it raises more questions than it answers. For example, do ALS patients carrying the *APOE* risk allele have more amyloid deposition or are other protein species involved? Why is the *APOE* ε2 allele a risk factor for FTD, when it is thought to be protective in other neurodegenerative diseases? Why do some patients carrying the *APOE* risk factor not develop dementia?¹⁴ Does this suggest the existence of additional risk or even protective factors elsewhere in the genome? Genome-wide studies would be the ideal way to search for such loci, but such studies will be challenging due to the multiple testing involved, the requirement for large sample sizes, and the difficulty in interpreting how these multiple hits are operating within the CNS. A complex problem indeed, but an important one to address if we are to arrive at a better understanding of neurodegeneration. Therein lies the rub.

Acknowledgments

This work was supported by the Intramural Research Programs of the NIH, National Institute on Aging (Z01-AG000949-02).

References

1. Lillo P, Hodges JR. Frontotemporal dementia and motor neurone disease: overlapping clinic-pathological disorders. *J Clin Neurosci*. 2009; 16:1131–1135. [PubMed: 19556136]
2. Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science*. 2006; 314:130–133. [PubMed: 17023659]

3. Renton AE, Majounie E, Waite A, et al. ITALSGEN Consortium. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron*. 2011; 72(2): 257–268. [PubMed: 21944779]
4. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron*. 2011; 72(2):245–256. [PubMed: 21944778]
5. van Blitterswijk M, Mullen B, Nicholson AM, et al. TMEM106B protects C9ORF72 expansion carriers against frontotemporal dementia. *Acta Neuropathol*. 2014; 127(3):397–406. [PubMed: 24385136]
6. Chiò A, Brunetti M, Barberis M, et al. The role of APOE in the occurrence of frontotemporal dementia in ALS. *JAMA Neurol*. In Press.
7. Govone F, Vacca A, Rubino E, et al. Lack of association between APOE gene polymorphisms and amyotrophic lateral sclerosis: a comprehensive meta-analysis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2014; 15(7–8):551–556. [PubMed: 24918518]
8. Li YJ, Pericak-Vance MA, Haines JL, et al. Apolipoprotein E is associated with age at onset of amyotrophic lateral sclerosis. *Neurogenetics*. 2004; 5(4):209–213. [PubMed: 15657798]
9. Siddique T, Pericak-Vance MA, Caliendo J, et al. Lack of association between apolipoprotein E genotype and sporadic amyotrophic lateral sclerosis. *Neurogenetics*. 1998; 1(3):213–216. [PubMed: 10737125]
10. Piemonte and Valle d'Aosta Register for Amyotrophic Lateral Sclerosis (PARALS). Incidence of ALS in Italy: evidence for a uniform frequency in Western countries. *Neurology*. 2001; 56:239–244. [PubMed: 11160962]
11. Trojanowski JQ, Lee VM. Brain degeneration linked to "fatal attractions" of proteins in Alzheimer's disease and related disorders. *J Alzheimers Dis*. 2001; 3(1):117–119. [PubMed: 12214080]
12. Hensman Moss DJ, Poulter M, Beck J, et al. C9orf72 expansions are the most common genetic cause of Huntington disease phenocopies. *Neurology*. 2014; 82(4):292–299. [PubMed: 24363131]
13. Gwinn-Hardy K, Singleton A, O'Suilleabhain P, et al. Spinocerebellar ataxia type 3 phenotypically resembling parkinson disease in a black family. *Arch Neurol*. 2001; 58(2):296–299. [PubMed: 11176969]
14. Corder EH, Saunders AM, Risch NJ, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nat Genet*. 1994; 7(2):180–184. [PubMed: 7920638]