

What is missing in ALS



Haploinsufficiency is a well studied mechanism of disease. In this issue of *The Lancet Neurology*, Blauw and colleagues¹ report an excess of deleted genes that is specific to patients with amyotrophic lateral sclerosis (ALS), which implies haploinsufficiency. The evidence for this excess came from mining for copy number variants (CNVs) in data from previous genome-wide studies.^{2,3} These studies, in which over 300 000 single nucleotide polymorphisms (SNPs) were genotyped in 461 patients with sporadic ALS and 450 controls, recorded association of sporadic ALS with *ITPR2* and with *DPP6*. In their new study, the same researchers report an association between sporadic ALS and gene-centred deletions ($p=2.15 \times 10^{-12}$). However, this relative aggregation of heterozygous deletions in genes rather than in intergenic regions might result from a random process because the numbers of CNVs (deletions or duplications) did not differ between patients and controls.

CNVs have been reported in other disorders, including spinal muscular atrophy (deletion in *SMN* genes), Parkinson's disease (duplication in *SNCA*), and Charcot-Marie-Tooth 1A (large duplications involving *PMP22*). Blauw and colleagues did not show a signature pattern of gene deletion in sporadic ALS, but they did report categories of cellular function to which those genes belong. The researchers did not address compensatory gene expression in response to gene deletion, or qualitative or quantitative changes in proteins, which could have been important ways to validate or reduce the number of candidate genes. 14 of the 155 ALS-specific deleted genes were deleted in more than one patient, implying either that ALS has myriad individual genetic

causes or that the deletions are private polymorphisms. The study would have been more robust if the number of controls had matched or been twice that of patients. The script developed to analyse areas of duplication or deletion should also be independently validated and, as for all association studies, the preliminary results from this study should be verified in independent cohorts.

This report is the sixth genome-wide study of sporadic ALS but, unfortunately, the *APOE* equivalent for ALS has not been identified. The five previous genome-wide SNP studies²⁻⁶ showed either no association⁵ or an association that could not be validated.⁴ Blauw and co-workers initially reported the association of sporadic ALS with *ITPR2* in a Dutch cohort,² and the association with *DPP6* was detected when data from a North American study were included.³ This result was replicated in a cohort of Irish patients,⁶ but the odds of developing ALS associated with *DPP6* are small, and in 1000 individuals sporadic ALS was not shown to be associated with *FLJ10986* by use of 73 gene-specific SNPs, or with *DPP6* by use of 43 gene-specific SNPs and correction for multiple testing (unpublished). Blauw and colleagues¹ did not detect the previously reported association of ALS to deletions in *SMN1*. Another study also failed to show this association,⁷ underlining the need for large cohorts and replication.

Candidate-gene studies do not have a stellar record in ALS either. Replication failed to associate *APOE*, *VEGF*, *PVR*, or *ANG* across populations. An exception is the *PON* cluster of genes on chromosome 7, which has been replicated in five populations.⁸⁻¹¹ Unfortunately, the effect size is small.

Lack of replication and small effects of associated alleles are obvious problems in the understanding of complex

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disorders. The picture in sporadic ALS might become clearer after combined analysis of all available genome-wide data. However, if the effect size (odds ratio) remains small, very many risk genes would be implicated. How those low risks would add up to sporadic ALS with a lifetime risk of 1 in 600–800 is unclear. Is there an amplifying factor, or is the risk multiplicative? Perhaps ALS investigators should test for gene–gene and gene–environment interactions. If the deletions have pathogenic effects, then patients and their parents should be tested for parent-specific origins of the ALS-specific deletions. Epigenetic factors and post-translational random effects that cause conversion and amplification of pathological protein conformations should also be investigated. So far, the success of genome-wide studies in sporadic ALS has been minor, and a hard look at novel causes for ALS is needed.

Teepu Siddique

Northwestern University Feinberg School of Medicine, Tarry Building, 303 East Chicago Avenue, Chicago IL 60611, USA
t-siddique@northwestern.edu

I have no conflicts of interest.

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