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A roadmap for genetic testing in ALS

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Up-to-date guidelines help neurologists and ALS patients determine when genetic testing might be appropriate and how best to interpret results.

Chiò and colleagues present a new set of clinical suggestions for the genetic counseling and testing of patients diagnosed with amyotrophic lateral sclerosis (ALS).¹ The paper provides sage, straightforward advice for neurologists faced with questions from patients or their relatives about their risk of developing this fatal neurodegenerative disease and the role of genetic testing in quantifying that risk. Key among their recommendations is that mutational screening be extended to include more recently discovered genes. Furthermore, genetic testing should be discussed with all patients diagnosed with ALS, regardless of their family history. In so doing, the authors highlight the growing awareness among both the medical community and patients as to the predictive power of modern genomics.

Recent advances in our understanding of ALS genetics make these updated clinical suggestions particularly timely. The genetic aetiology of two thirds of familial ALS cases and approximately 10% of the more common sporadic form of the disease has now been worked out. The recent discovery of the pathogenic hexanucleotide repeat expansion in *C9ORF72* has been a game changer, not just because it accounts for such a large proportion of cases but also because it genetically unifies two clinically disparate neurological syndromes, namely, ALS and frontotemporal dementia.^{2,3} Current estimates suggest that as many as one in nine Caucasian ALS patients will carry the hexanucleotide expansion. In recognition of these advances, the new set of clinical suggestions broadens the number of genes that should be considered when pursuing testing of ALS patients.

The new guidelines also widen the scope of who should be tested, again reflecting our improved understanding of the genetic aetiology of the disease. *C9ORF72* is responsible for ~7% of sporadic ALS cases in Caucasian populations, representing the first time that a genetic cause has been found in more than just the occasional case of the commoner form of ALS.^{4,5} Although categorisation of ALS patients as familial or sporadic based on their family history retains some clinical utility, it is clear that the underlying biology is more nuanced and that such clinical classification should not be viewed in absolute terms.⁶ The Italian group put forward suggestions for genetic testing that recognise this fundamental shift in our understanding of the disease, and fully incorporate this concept into their guidelines.

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Competing interests

BJT has a patent pending on the clinical testing and therapeutic intervention for the hexanucleotide repeat expansion of *C9ORF72*.

The pace of gene discovery in ALS has dramatically accelerated, and many more causative genes will undoubtedly be identified in the near future. As a consequence, flexibility must be a central principle in any set of guidelines so that new information about the aetiology of the disease can be incorporated in a timely manner. Gene therapy targeting specific mutations may also become a reality over the next number of years, and the availability of effective personalised therapies will drastically change our approach to genetic testing, not just of patients, but also of asymptomatic relatives. Hence, annual review, which is the concluding recommendation of the authors, may even be the most cogent suggestion that they put forward.

The authors, a multidisciplinary group of Italian neurologists, geneticists and ethicists, are to be applauded for taking the initiative in drawing up this set of clinical suggestions. Their common sense approach to genetic testing will be of great value to neurologists caring for ALS patients. However, there is considerable country-to-country variability in genetic counseling and genetic testing, to the point that one size may truly not fit all. As we move forward into the postgenomic era, there is a growing need for a more comprehensive meeting involving neurologists and other specialists from around the world to debate the role of genetic testing in clinical care, and hopefully to achieve consensus on how to proceed.

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