

How much of the missing heritability of ALS is hidden in known ALS genes?

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Further research of rare variants in ALS genes is needed to guide diagnosis and counseling of patients

Over the last decade, our knowledge about the heritability of Amyotrophic Lateral Sclerosis (ALS) has greatly improved. More than 25 genes have been associated with ALS.¹ Some gene mutations segregate with high penetrance in people with familial ALS, some genetic variants have a lower penetrance or merely act as ALS risk alleles. With all of these genes roughly 40%–80% of familial ALS, but also 5%–15% of sporadic ALS can be explained. Indeed, in patients with sporadic ALS, a genetic component is also present: the estimated heritability of sporadic ALS is about 60%.² This suggests that the genetic architecture of ALS is complex and consists of a mixture of gene mutations that differ in noxiousness and in frequency. At the same time, it is clear that there is considerable missing heritability. With the advent of next generation sequencing technology, more and more rare genetic variants are being identified in known ALS genes and it is often challenging to classify such variants as pathogenic or benign.

In the *JNNP* paper by Müller *et al*³, the results of a comprehensive analysis of known ALS genes in a cohort of 301 German ALS families are presented. In about half of these, a pathogenic mutation could be identified, mostly in the genes *C9orf72*, *SOD1*, *FUS*, *TARDBP* or *TBK1*. This suggests that these are the top genes that should be offered in the diagnostic setting in central Europe. In addition, several previously unreported variants were found in known ALS genes. On the basis of stringent criteria, the authors classified these as pathogenic, likely pathogenic or as variants of unknown significance.

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Other recent studies in ALS populations from the UK and the Netherlands also identified an increased burden of rare variants in known ALS genes, in the coding regions and in the untranslated regions.^{4–6} Interestingly, there are also patients with combinations of rare variants in known ALS genes. This suggests that ALS can be caused by a single highly penetrant mutation or a combination of a few less penetrant rare variants. Hence, ALS appears to have an oligogenic origin.

Further research is needed to establish the exact level of pathogenicity at the single variant level of all genetic variation in ALS genes and to establish if combinations of rare variants can cause ALS. A global whole genome sequencing project, aiming to sequence 15 000 patients with ALS and 7500 controls under the banner of Project MinE (<http://www.projectmine.com>) will help to answer some of these questions and to uncover missing heritability within known ALS genes.

Detailed information about the risk of each variant is also crucial with regard to the counselling of patients and their families. Straightforward counselling is only possible for established pathogenic mutations. The complexity of counselling will only continue to increase, as more patients with combinations of rare variants will be seen, due to the increased use of next generation sequencing technologies in a diagnostic setting.

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