Is all ALS genetic?

In this issue of Neurology®, Gibson et al.¹ address an important issue in amyotrophic lateral sclerosis (ALS) genetics: namely, what percentage of isolated or sporadic forms of ALS that have an identifiable genetic factor are likely responsible for disease pathogenesis.

To address this, the authors used a 3-step approach: first, they selected 87 patients they diagnosed with sporadic ALS (SALS) and who were of European ancestry (to get as a homogenous a study cohort as possible). They then screened the exons of all 23,000 genes, focusing on variants in the 31 genes earlier linked to ALS, as well as 2 repeat intron sequences in the C9orf72 and ATXN2 genes also known to cause ALS. As with the general population, the patients harbored several genetic variants. The critical question is as follows: which of them are pathogenic?

To address this, Gibson et al. used a panel of validated pathogenicity-prediction computer models to exclude a third of the observed variants in the selected 33 ALS genes. This approach is the real novelty of the present study: all earlier studies of genetic variants in SALS have simply compared the frequency of observed variants in patients with a matched control population. While the DNA screening revealed that 28.7% of the 87 patients with SALS carried any variant in the 33 genes, only 17.2% carried a probable ALS-pathogenic mutation when a joint approach, utilizing both allele frequency and variant pathogenicity prediction, was applied. The relative effect of ALS-associated genes is stronger when variant pathogenicity is considered instead of only variant rarity. This is a critical observation in this study, but of course relies on the sensitivity and specificity of the used prediction models to determine pathogenicity.

However, this finding leads to another observation: despite extensive genetic and statistical analysis of a highly defined SALS cohort, only a fifth of the SALS group had an identifiable probable generic cause among the studied 33 genes. This should not be taken as evidence that genetics do not play a predisposing role for the majority of SALS cases, just that we are not yet able to reveal it despite using sophisticated second-generation sequencing technologies. There is ample emerging evidence that the architecture of the genome plays a role in deciding who gets ALS and who does not.² In this context, other researchers have found evidence for other variants that reduce the risk of an individual for ALS, such as deletions of SMN2, or specific variants in PGC-1α or CHGB.³ Such neuroprotective variants were not studied in the present study.

So why did Gibson et al. find that 17% of their patients with SALS carried a pathogenic genetic variant in one of the 33 known ALS-causing genes? Hereditary ALS is now recognized as a heterogeneous syndrome with multiple subtypes and different modes of inheritance. The classical Mendelian dominant mode of inheritance with high penetrance is easily recognized and accounts for most of the 5% of ALS cases categorized as familial ALS in epidemiologic studies. However, dominant inheritance with reduced penetrance is more difficult to detect: there can be several close family members who, like the patient with ALS, are mutant carriers, but remain asymptomatic throughout life. In fact, we have found families where there are far more carriers of a definite pathogenic variant than there are patients with ALS, but transgenic animal studies of the variant and laboratory studies still support that such variants are pathogenic.⁴ The third mode of inheritance is recessive, and so far for adult-onset ALS this has only been established firmly for the p. Asp91Ala SOD1 mutation, the most commonly found SOD1 mutation worldwide and the second-most common identified cause of ALS overall.⁵ With families becoming smaller, it is less likely that a recessive trait will be revealed in 2 siblings. Most patients with ALS homozygous for p. Asp91Ala SOD1 therefore get a SALS and not familial ALS diagnosis. Two of the 87 patients with SALS carried the p. Asp91Ala SOD1. The fourth mode of inheritance is oligogenic inheritance, where the patient with SALS has inherited different gene defects from both parents. With the present state of knowledge, such cases are rare, but surprisingly, 2 of the 87 studied patients with SALS in the present study carried 2 bad genes (neither had the same combination). The fifth mode is the occurrence of somatic de novo mutations. This has been found in a few SALS cases with FUS, TDP43, or

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SOD1 mutations when samples have been available from the parents for comparison, to prove paternity (in the present study, no parental samples were studied). The sixth mode of inheritance is pleiotropism, i.e., the same gene variant may give rise to different phenotypes (diagnosis). It is now increasingly recognized that variants in several of the genes initially linked to ALS may also predispose to other diseases, most notably frontotemporal dementia, cerebellar degeneration, olivopontocerebellar atrophy, or Paget disease, frequently masking the genetic predisposition for ALS.

In this context, a recent discovery is noteworthy: injection of seeds of misfolded mutant human SOD1 into the spinal cord of mice elicits a fulminant murine ALS disease with templated propagation of misfolded SOD1 prion-like species through the motor neuraxis. Two different pathogenic strains of misfolded SOD1 species were studied, resulting in different ALS phenotypes in the mouse models: surprisingly, human mutant p.Asp91Ala SOD1 could develop ALS in either of the 2 strains, showing that genetics is influenced by other factors. Potentially, this enucleation process of SOD1 species could occur in other parts of the CNS, explaining the rare occurrence of frontotemporal dementia associated with SOD1 mutations.

The study by Gibson et al. sheds further light on the ongoing neurogenetic revolution, but emphasizes with the study by Bidhendi et al. that nongenetic factors probably play an important role as well.

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REFERENCES