The underestimation of familial ALS and counseling patients with sporadic ALS

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Amyotrophic lateral sclerosis (ALS), the most common degenerative disease of the adult motor neuron system, occurs sporadically in 90% to 95% of cases. This implies no affected relative and no association with 1 of the 3 western Pacific foci.[1] While "any affected relative," the opposite of "no affected relative," might be considered the definition for familial ALS (fALS), 2 or more remotely related members of an extended family might have sporadic ALS (sALS) due to chance alone. Conversely, a case of sALS might be a case of fALS, not recognized as such because of an incomplete family history or incomplete penetrance in ancestors. Because most forms of fALS are autosomal dominant, making the distinction between fALS and sALS has profound implications in counseling relatives of patients with sALS. Discussions of clinical definitions of fALS have focused on 2 questions: the smallest number of affected relatives required to define fALS (2 or more?) and the degree of relatedness (first, second, any?).[2]

In this issue of *Neurology*®, Gibson et al.[3] tried to determine how far in a family tree there is apparent excess of disease in relatives of probands with ALS. This answer may inform the clinical definition of fALS. They analyzed death certificates from 1904 to 2009 from patients with at least 3 generations recorded in the Utah Population Database, a genealogic and medical database of more than 2 million Utah residents. They compared the risk of dying of ALS in relatives of patients with ALS relative to control cohorts and found that the relative risk was 4.91 in first-degree relatives and 2.85 in second-degree relatives but that it was not increased among third- to fifth-degree relatives. This result supports a clinical definition of fALS that includes up to second-degree relatives. The authors concluded that the frequency of fALS is 3.7% if at least one affected first-degree relative is required for the definition and 8.6% if second-degree relatives are included. The results cannot be used to advise individuals who present with sALS regarding their risk of having fALS because the methods used cannot provide data on the frequency with which family links unknown previously were revealed.

Other studies used a cohort approach to estimate the risk to relatives of patients presenting with sALS. At a tertiary referral center in London, UK, first-degree relatives of patients with sALS were followed prospectively.[4] By age 85 years, siblings were found to have an 8-fold increased risk of developing ALS and the likelihood of remaining unaffected decreased from 99.7% to 97.6%—a lifetime risk of 2.4%. The annual risk of developing disease was similar in siblings and offspring. A cohort study based on the Swedish Multi-Generation Register,[5] where the probands were individuals who were the first in their families to be identified with ALS, found a 10-fold increased risk of developing the disease in first-degree relatives. However, the methods of this study also could not distinguish between known fALS families and individuals thought to have sALS.

Genetic testing may provide a different approach to answering these questions. The genes underlying more than 50% of fALS cases have been identified. Previously, genes underlying fALS were found only rarely (<1%) in sporadic cases. However, a cause of fALS identified recently—a hexanucleotide repeat expansion in *C9orf72*—occurs in 7% of white individuals of European descent with sALS, with an age-dependent increase in penetrance.[6] The frequencies are lower in individuals not of European descent, as the founder risk haplotype is from Finland. A 7% carrier rate in white individuals of European descent with sALS translates into a lifetime risk of 3.5% for first-degree relatives who live to age 80 years, similar to the 2.4% estimate from London.[4]

Frontotemporal dementia (FTD), in both familial and sporadic forms, may also be caused by the *C9orf72* hexanucleotide repeat expansion in some patients, and there is an overlap of the ALS/FTD clinical phenotypes. The expanded repeat occurs in 6% of individuals with sporadic FTD.[6] Additional genes are involved in familial and, to a lesser extent, in sALS and FTD.[7–9] Expanding fALS to include individuals with sALS and a family history of FTD[2] increases the frequency of fALS, yet still within the 5% to 10% range, but reduces the likelihood of an abnormal gene in remaining truly sALS patients.

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While 2.4% to 3.5% may be a tentative current estimate of the risk to first-degree relatives of individuals with sALS of white European ancestry whose gene status is unknown, the risk is smaller in individuals of other ancestry. These estimates will change as some individuals are reclassified as fALS. If patients are determined to be gene carriers, the lifetime risk increases to 50% in their first-degree relatives. The risk to first-degree relatives of known non–gene carriers moves closer to the background risk, but does not attain it, as genes that have not yet been identified likely have a part in rare cases of sALS.

Some patients with sALS, no family history suggesting FTD, and unknown gene status may not be satisfied with a tentative 2.4% to 3.5% lifetime estimate of risk to their first-degree relatives and may seek greater resolution by determining their gene status. The implications to relatives are greater than those to affected patients, are far-reaching, and may affect their insurability. While determination of non–gene carrier status will be met with relief, identification of carrier status even in one family member creates extensive pressures on all relatives. Patients, families, and physicians who are considering genetic testing need to make sure that all affected parties are made aware of the ramifications and are included in discussions and counseling.

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