ALS genetic epidemiology ‘How simplex is the genetic epidemiology of ALS?’

Jan H Veldink

First, how genetic is amyotrophic lateral sclerosis (ALS)? We know that there are clear ‘Mendelian’ forms of the disease where the classic Mendelian rules of inheritance apply, and several first-degree and second-degree relatives are affected by the disease. Prospective population-based registries show that the rate of this Mendelian form of ALS is about 5% (and not 10% as most often is assumed).1 The far majority of patients, therefore, cannot be classified as such, but twin studies in ALS have shown that genetics explain about 61% of liability in ALS, suggesting that a substantial genetic contribution is available for discovery, even in patients with no family history.2 Also, patients with ‘sporadic’ ALS show mutations in major ALS genes.

In their JNNP manuscript, Zou et al3 very elegantly describe the genetic epidemiology of sporadic and ‘familial’ ALS, applying a clear definition for familial versus sporadic disease.4 Using guidelines for meta-analyses and systematic reviews, the authors have screened over 6000 articles dealing with mutation frequencies in the ‘big four’ in ALS: C9orf72, SOD1, TARDBP and FUS.

There are three important observations to take home from this huge effort.

First, Asian and European ALS cohorts show a striking divergent genetic background, which is not due to publication bias. The most common ALS mutation in European patients, both sporadic and familial, is the C9orf72 repeat expansion, while non-synonymous mutations in SOD1 are the most common mutations in Asia. Frequencies of C9orf72 mutations in familial disease were most common in Belgium and Greece (both 50%), followed by Finland (46.4%), while SOD1 mutations were highest in Korean (54.7%), Russian (50%) and Finnish (42.9%) cohorts. This shows that the genetic origin of ALS in different populations is not uniform across the globe and suggests the occurrence of many independent founder mutations in the past, as has been shown with the common risk haplotype in C9orf72 repeat expansion carriers.1,6 The consequence of this finding is that genetic testing in European populations need to first focus on C9orf72 using a combination of repeat-primed PCR and fluorescent PCR, while in Asian populations, non-synonymous mutation screening in SOD1 (and other ALS genes) is the first step.

Second, the authors also show through meta-regression that besides population type (Asian vs European), the type of cohort (population-based vs hospital based) is a strong determinant of mutation frequencies. This suggests that population-based cohorts provide less biased estimates compared with hospital-based series, since these are typically characterized by younger patients, a phenomenon well known in ALS epidemiology.

Last, this paper again shows strong indications for the existence of an oligogenic basis for ALS: the co-occurrence of two mutations in the big four was 0.4% in familial ALS, which is much higher compared with expected by chance. It mostly concerned combinations between TARDBP, FUS or SOD1 with C9orf72 repeat expansions.

What can we learn from these observations?

Recent insights show that the genetics of all ALS (both sporadic and familial) is characterized by a disproportionate contribution of rare genetic variation, as opposed to common complex diseases such as schizophrenia,7 and population-based incidence figures appear to fit well with a so-called discrete multistep process.8 Indeed, rare genetic variation is much more geographically stratified compared with common genetic variation, which is in agreement with the findings in ALS by Zou et al.9 The combination of the importance of rare genetic variation with a multistep model suggests that ALS is somewhere in between common complex diseases and simple Mendelian diseases. In that sense, ALS can be regarded as a ‘simple’ disease. Given the strong influence of geography, rare genetic variation and study type in assessing mutation frequencies, this truly calls for a global effort to do ALS genomics. We need to include more populations from countries that are traditionally under-represented in large genomics efforts. The samples are there, the international expertise is there, the ICT solutions are there, but there are still a number of challenges that need to be met: setting up prospective cohorts in many countries to collect biosamples and clinical data, getting proper informed consent on all samples, so these can be used for research purposes and last but not least, funding to generate the data. Recent crowdfunding events have shown how successful these can be to generate funds (swimming, hiking or cycling for ALS).

With the advent of gene-specific therapies, this seems to be an urgent matter for all patients with ALS.

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