Common genetic variants and the heritability of ALS

Ammar Al-Chalabi1* and Peter M. Visscher2,3

1. King’s College London, Institute of Psychiatry, Department of Basic and Clinical Neuroscience, London SE5 8AF, UK (*corresponding author)
2. Queensland Brain Institute, University of Queensland, Brisbane, Queensland, Australia
3. The Translational Research Institute, University of Queensland Diamantina Institute, Brisbane, Queensland, Australia

Biographies:

Ammar Al-Chalabi is Professor of Neurology and Complex Disease Genetics at King’s College London, UK, and Director of the King’s MND Care and Research Centre at King’s College Hospital. He is a clinician-scientist with a specific interest in genetic and other risk factors for ALS, and their effect on phenotype. His recent work includes quantifying the risk to patients and relatives of people with ALS through twin studies, epidemiological studies, statistical modelling, and multinational genome-wide association and sequencing studies. He currently coordinates an EU JPND-funded Europe-wide programme to identify risk and modifier factors in ALS by stratifying ALS phenotypes.

Peter Visscher is Professor of Quantitative Genetics at the University of Queensland, and Director of the Centre for Neurogenetics and Statistical Genomics. His research is at the interface of quantitative genetics, statistical genetics, population genetics, human genetics, evolution, bioinformatics and genetic epidemiology. His current research focuses on estimation and dissection of complex-trait variation in human populations, through the development of new statistical genetics methods for estimation and prediction, and applications to quantitative traits and disease in human populations.
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Amyotrophic lateral sclerosis shows complex inheritance. A new study replicates previous estimates of the heritability due to common genetic variation and suggests possible disease-associated loci. Despite such efforts, our understanding of the genetic architecture of amyotrophic lateral sclerosis remains limited.

In any one person, amyotrophic lateral sclerosis (ALS) may be caused by environmental factors acting in concert with a single gene (monogenic), a few genes (oligogenic), or many (polygenic), with implications for genetic counselling and other information given to patients. One measure of the degree by which genetic variation influences the risk of a disease is heritability (BOX). An analysis by Keller and colleagues\(^1\) of three genome-wide association studies (GWAS) comprising 1,223 ALS cases and 1,591 controls reported a heritability estimate for ALS using a method called GREML, implemented in the genome-wide complex trait analysis software package GCTA.\(^2\)

An estimate of heritability is important to assess whether genetic variation influences the risk of ALS in people with no apparent family history. It does, as previously quantified from the risk of relatives,\(^3\) heritability estimates from pedigree data\(^4,5\) and from unrelated individuals using SNP data,\(^6\) oligogenic and Mendelian mimics of sporadic ALS,\(^7,8\) statistical models,\(^9\) consistency of diagnosis of familiality\(^10\) and the finding of Mendelian ALS genes in those with apparently sporadic ALS (http://alsod.iop.kcl.ac.uk). Quantifying and dissecting heritability allows us to counsel patients effectively and know where to focus our research efforts. In the context of GWAS, it quantifies the contribution of variation from common SNPs that can be identified using larger experimental sample sizes.
Keller and colleagues report heritability as 21%, and contrast this with the result from an earlier study that reported an estimate of 12% from a larger set of 6,100 sporadic cases and 7,125 controls, that partly overlaps with the current study, and used identical methods. These estimates can be reconciled by noting that in addition to sampling variation, the two studies used different prevalences: 10 per 100,000 person-years for the study by Keller and colleagues, and 5 per 100,000 for the earlier study. Indeed, the earlier study also estimated heritability of liability as 21% at a prevalence of 10 per 100,000.

It is important to clarify that what Keller and colleagues report is not in fact the heritability of ALS, but rather the heritability of ALS that is captured by considering all common SNP variants simultaneously. ALS heritability estimates from twin studies are 76% (95% confidence interval 60%, 86%) when all cases are included and 61% (95% confidence interval 38%, 78%) when familial cases are excluded, and in family studies they range from 40% to 60%: the twin and family studies estimate the total heritability of which part is due to common SNP variants. The remaining "hidden" heritability is likely to be found in rare variants, and other genetic variations such as copy number variants that are not captured by common SNPs. When heritability is estimated from pedigree data (e.g. in a twin study), it is blind with respect to the allelic spectrum of causal variants in the population. In contrast, heritability estimated from SNP data (as in this study) depends on the underlying genetic architecture. The contribution of low frequency variants, with a frequency of, say, less than 1 in 1000, will not be captured from GWAS data whereas it will in a pedigree study.

The authors used samples from three groups: people with apparently sporadic ALS from an outbred Italian population, and samples from people with familial or sporadic ALS from a speciality clinic in Finland (a genetically homogeneous population), and from US based speciality clinics. One might expect the heritability estimate to differ between familial and sporadic samples and in this regard it is interesting that the heritability appeared the same in all three cohorts. This finding underlines
previous work showing that the distinction between familial and sporadic cases is ambiguous, because clinicians are not uniform in their definitions,\textsuperscript{10} the probability of more than one person being affected depends on family size and penetrance,\textsuperscript{9} and there is an increased risk to relatives of those with sporadic ALS, probably because of oligogenic and polygenic effects.\textsuperscript{3, 8} The finding is also consistent with twin studies that show little change in heritability estimates with the inclusion or exclusion of familial samples.\textsuperscript{4, 5}

A key and novel finding reported by Keller and colleagues is of genomic regions explaining a significant proportion of variation, and therefore possibly harbouring ALS genes. The authors used 20Mb segments of the genome and applied GREML methods to each segment in each population, with regions of interest then broken down into 1Mb regions for further analysis.\textsuperscript{2} Results were then meta-analysed across the three populations. This is an interesting strategy, and an alternative to standard association testing using individuals SNPs, but requires care in interpretation, since 20 Mb regions can soak up variation from nearby regions due to linkage disequilibrium.

This study replicates previous work on ALS heritability captured from common SNPs and confirms existing ideas about the role of genetic variation in apparently sporadic ALS.\textsuperscript{6} The estimates from the current and previous study are consistent and point to a role of common variants in ALS. The heritability explained from the few GWAS hits to date is less than 1\%, implying that many more common loci are still to be found and that these can be detected when larger experimental sample sizes are used. Our understanding of the genetic architecture of ALS has been transformed in recent years by advances in genetic technologies, statistical and computing approaches to genetics, and our knowledge of the genome. Clinicians may find it difficult to keep up with such a rapidly changing field, but the message to our patients must remain based in evidence and consistent: there is a genetic component to ALS, but it varies in degree between people; the risk to relatives of someone with no family history remains small; and until there are effective therapies, genetic testing of
affected individuals with no family history should only be undertaken after very careful consideration of the consequences.

**BOX**

Heritability is not the same as "genetic contribution". It is the proportion of phenotypic variance explained by genetic variance and can be estimated using different experimental designs.

The heritability of having a head is zero, because there is no phenotypic variance (everyone has a head), even though having a head is clearly completely genetically determined.

Heritability applies to populations, not individuals. Knowing the heritability of ALS tells us nothing about the genetic contribution to disease in an individual, or in a population of different ethnicity.

For a quantitative trait, such as height, the phenotypic variance can be estimated from a population sample. For a discrete trait, such as ALS, geneticists assume an underlying liability to disease that is normally distributed and includes genetic and environmental components; only individuals carrying enough liability develop disease. Variation in observed risk reflects population prevalence, and is related to heritability on the risk scale.11
References


