An estimate of amyotrophic lateral sclerosis heritability using twin data

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ABSTRACT

Background Causative gene mutations have been identified in about 2% of those with amyotrophic lateral sclerosis (ALS), often, but not always, when there is a strong family history. There is an assumption that there is a genetic component to all ALS, but genome-wide association studies have yet to produce a robustly replicated result. A definitive estimate of ALS heritability is therefore required to determine whether ongoing efforts to find susceptibility genes are worth while.

Methods The authors performed two twin studies, one population- and one clinic-based. The authors used structural equation modelling to perform a meta-analysis of data from these studies and an existing twin study to estimate ALS heritability, and identified 171 twin pairs in which at least one twin had ALS.

Results and discussion Five monozygotic twin pairs were discordant-affected, and 44 discordant-affected. No dizygotic twin pairs were discordant-affected, and 122 discordant-affected. The heritability of sporadic ALS was estimated as 0.61 (0.38 to 0.78) with the unshared environmental component 0.39 (0.22 to 0.62). ALS has a high heritability, and efforts to find causative genes should continue.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of motor neurons with a median survival of about 2 years. The lifetime prevalence is about 1 in 400, but the appalling prognosis means that the point prevalence is only 5 per 100 000 persons. In 95% of cases, there is no family history of ALS, but a study has found that the risk to siblings or offspring of a proband is elevated between nine and 17 times. There is thus a familial tendency to ALS, which is best regarded as a complex disease.

There have been many genetic studies of ALS, but the only consistent findings have been the identification of six genes in which mutation predisposes to ALS, both in families and in sporadic cases, accounting for about 2% of ALS overall; these are SOD1, TARDBP, FUS, VAPB, ANG and OPTN. Genome-wide association studies have not resulted in independent replication of findings, although replication of a large study in a second large internal cohort has been successful. There is, nevertheless, the assumption of a genetic component to all ALS. A twin study would help determine whether this assumption is reasonable by allowing an estimate of ALS heritability. The British Motor Neuron Disease (MND) Twin Study made a start on this process by reporting the likely range in which the ALS heritability value would lie: 0.38 to 0.85. We have therefore collected twin data from two further sources: the Swedish Twin Registry and the King’s College Hospital Motor Neuron Disease Clinic Register. We have analysed these two new data sets with the existing data used for the British MND Twin Study, independently but simultaneously in a meta-analysis framework, to generate for the first time an estimate of ALS heritability.

METHODS

Data collection

Data for the British MND Twin Study were extracted from the published manuscript. Methods for the Swedish Twin Registry and King’s Register have been previously described. For the King’s Register, pedigree records as obtained at the initial visit of each participant were used to identify twins. Zygosity status was self-reported, a method shown in the Swedish Twin Registry to be correct in 99% of twin pairs. Concordance was defined as reported in the pedigree at the time of last follow-up. The two new studies were approved by the Research Ethics Committees of each institution. Informed written consent to participate in research was obtained for all participants.

Familiality

Although the distinction between familial and sporadic ALS is to a large extent artificial, the population under study consists of two groups: those with a strong family history of ALS in whom we can assume a strong genetic component, and those without, in which the demonstration of a heritable component would be most useful. We therefore tested the effect of including and excluding individuals with a family history of ALS in a first-degree relative. For the British MND Twin Study, this information was provided in the published information. For the Swedish Twin Registry, data were linked to the Swedish Multi-Generational Register, which has family history information for those born after 1932 who were still alive in or after 1967, the Swedish Inpatient Register (1973 to 2004) and the Swedish Causes of Death Register (1961 to 2005) to identify relatives with ALS. For the King’s Register, pedigree structure and family history taken both at the initial visit and at subsequent follow-up were used to identify families with affected first degree relatives.

Statistical methods

Genetic model-fitting is based on biometrical genetic theory where contributions of additive genetic (A), dominant genetic (D), shared environmental (C) and unshared environmental (E) effects on the trait are estimated by examining how often twins of different types correlate. Monozygotic
Genetic model-fitting results: variance components (with 95% CI)

<table>
<thead>
<tr>
<th>Genetic model</th>
<th>Twins included</th>
<th>Modeled as next dizygotic pair concordant</th>
<th>Additive genetic component (A)</th>
<th>Common environmental (C) or dominant genetic (D) component</th>
<th>Unique environmental component (E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADE</td>
<td>All</td>
<td>No</td>
<td>0.00 (0.00 to 0.80)</td>
<td>0.73 (0.00 to 0.85)</td>
<td>0.27 (0.15 to 0.45)</td>
</tr>
<tr>
<td>AE</td>
<td>All</td>
<td>No</td>
<td>0.71 (0.53 to 0.84)</td>
<td>--</td>
<td>0.29 (0.16 to 0.47)</td>
</tr>
<tr>
<td>ACE</td>
<td>All</td>
<td>Yes</td>
<td>0.52 (0.04 to 0.85)</td>
<td>0.21 (0.00 to 0.58)</td>
<td>0.27 (0.15 to 0.45)</td>
</tr>
<tr>
<td>AE</td>
<td>All</td>
<td>Yes</td>
<td>0.76 (0.60 to 0.86)</td>
<td>--</td>
<td>0.24 (0.14 to 0.40)</td>
</tr>
<tr>
<td>ADE</td>
<td>Sporadic</td>
<td>No</td>
<td>0.00 (0.00 to 0.75)</td>
<td>0.64 (0.00 to 0.81)</td>
<td>0.36 (0.19 to 0.59)</td>
</tr>
<tr>
<td>AE</td>
<td>Sporadic</td>
<td>No</td>
<td>0.61 (0.38 to 0.78)</td>
<td>--</td>
<td>0.39 (0.22 to 0.62)</td>
</tr>
<tr>
<td>ACE</td>
<td>Sporadic</td>
<td>Yes</td>
<td>0.36 (0.00 to 0.80)</td>
<td>0.30 (0.00 to 0.63)</td>
<td>0.35 (0.19 to 0.57)</td>
</tr>
<tr>
<td>AE</td>
<td>Sporadic</td>
<td>Yes</td>
<td>0.70 (0.52 to 0.83)</td>
<td>--</td>
<td>0.30 (0.17 to 0.48)</td>
</tr>
</tbody>
</table>
(dropping C) showed an additive genetic component of 0.70 (0.52 to 0.83).

**DISCUSSION**

We estimate the heritability of sporadic ALS to be 0.61 (0.38 to 0.78). The strength of this study lies in the extra power available from combining the two new studies and the previous British study in a meta-analysis. This has allowed us to independently but simultaneously model the different studies, despite their different designs. The value we obtain and the confidence interval lie within the range predicted by the British MND Twin Study. Although it can be difficult to estimate heritability in relatively rare diseases, our study combines data from 10 872 MND death certificates over a 10-year period, a country-wide study of 86 441 twin pairs and a clinic-based study of 4982 individuals with ALS or their family members, generating results from 171 ALS twin pairs.

Our analysis differs from the British MND Twin study in an important aspect. We used structural equation modelling. This is a powerful likelihood-based technique that allows an estimate of heritability despite the lack of concordant-affected DZ twin pairs, without resorting to statistical workarounds. The British MND Twin study used an accepted method in which the next affected DZ twin observed is assumed to come from a concordant pair. When we adopted this approach, the results were not very different from our unmodified analysis (table I). This is important, as it suggests that a moderate increase in sample size designed to identify more twin pairs will not greatly change our results.

When familial samples were included in our analysis, the heritability estimate was, as expected, higher, but the overall findings are not greatly different from those for sporadic ALS, whether or not we allowed for the next DZ twins identified to be concordant-affected.

We have previously estimated the heritability of age of onset of SOD1-mediated ALS as 0.29 (0 to 0.42) using a variance components approach in ALS pedigrees. This contrasts with the much higher estimate for susceptibility heritability we obtain here, indicating independent genetic effects on age of onset and susceptibility.

Comorbidity of ALS and frontotemporal dementia, and pathological overlap is well recognised. No formal twin study has been performed for frontotemporal dementia, but in more than 41% of cases, there is some family history, suggesting a high heritability. We did not distinguish between individuals with and without frontotemporal dementia concurrent with ALS, and our heritability estimate will therefore also have implications for frontotemporal dementia.

This study has important implications for sporadic ALS. Clinically, the knowledge of a significant genetic component means that the question of why ALS has developed can be more confidently explained in terms of complex disease genetics. For research, despite the difficulties with replication of genome-wide association studies, we can pursue more highly powered genome-wide association studies boldly, explore statistical methods for interactions and epistasis, and use techniques to find rare genetic variants, copy number variants, microsatellites and epigenetic changes.

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**Competing interests** None.

**Ethics approval** Ethics approval was provided by the King's College Hospital and SLAM/IDP Research Ethics Committees for the UK participants. For the Swedish Twin Registry, the ethical advice from the Research Ethics Committee of the Karolinska Institutet was that specific approval was not required to use the data. For the British MND Twin Study (1997) we used published data.

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**REFERENCES**


