# Rate of familial amyotrophic lateral sclerosis: a systematic review and meta-analysis

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# Rate of familial amyotrophic lateral sclerosis: a systematic review and meta-analysis

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## ABSTRACT

**Background** The population rate of familial amyotrophic lateral sclerosis (FALS) is frequently reported as 10%. However, a systematic review and meta-analysis of the true population based frequency of FALS has never been performed.

**Method** A Medline literature review identified all original articles reporting a rate of FALS. Studies were grouped according to the type of data presented and examined for sources of case ascertainment. A systematic review and meta-analysis of reported rates of FALS was then conducted to facilitate comparison between studies and calculate a pooled rate of FALS.

**Results** 38 papers reported a rate of FALS. Thirty-three papers were included in analysis and the rate of FALS for all studies was 4.6% (95% CI 3.9% to 5.5%). Restricting the analysis to prospective population based registry data revealed a rate of 5.1% (95% CI 4.1% to 6.1%). The incidence of FALS was lower in southern Europe. There was no correlation between rate of FALS and reported SOD1 mutation rates.

**Conclusion** The rate of FALS among prospective population based registries is 5.1% (CI 4.1 to 6.1%), and not 10% as is often stated. Further detailed prospective population based studies of familial ALS are required to confirm this rate.

## INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease which was first described by Charcot in the mid-nineteenth century. It is predominantly a sporadic disease but a small percentage of cases occur within kindreds.[1]

In 1955, Kurland *et al* published a case series of 58 patients in which 10% reported a family history of ALS.[2] Although subsequent publications have reported varying rates of familial amyotrophic lateral sclerosis (FALS), the figure of 10% remains as the accepted population frequency of FALS.[3–7]

There is no definitive definition for FALS. It is generally accepted that the presence of ALS in either a first or second degree relative of the index case constitutes the familial form of the disease. Genes known to be associated with FALS include SOD1, TARDP, FUS and ANG.[8] The frequency of SOD1 mutations has been estimated to account for 10–20% of all FALS cases.[6] This estimate is not population based and most studies preferentially recruit patients with familial ALS.[9 10] To date only one population based estimate of SOD1 frequency has been carried out, reporting a rate of 13.6%.[11] Estimation of the rates of SOD1 related FALS is also confounded by the occurrence of mutations in up to 5% of the sporadic population, some of whom represent familial disease with incomplete penetrance.[12] The population frequency of the other known causative genes within populations has not been established.

We performed a systematic review and meta-analysis of all studies that presented original data reporting a rate of FALS (ie, the proportion of familial cases among all ALS cases, either in a defined population or in a case series). Analysis of the population based frequency of FALS was then undertaken and, where possible, a geographic comparison was made with the frequency of known SOD1 mutations.

## METHODS

### Systematic search

A Medline literature search was performed to identify all published studies on FALS, in addition to ALS incidence and prevalence studies from 1966 to October 2009. The MeSH terms 'ALS', 'amyotrophic lateral sclerosis', 'FALS', 'familial amyotrophic lateral sclerosis', 'familial motor neuron(e) disease', 'motor neuron(e) disease', 'MND', 'incidence', 'prevalence' and 'mortality' were used. Additional references were sought from cited articles. Where no information was reported on the rate of FALS in a population based study, the corresponding author was contacted where possible. Unpublished up to date data from the Irish ALS prospective population based register was also used.

### Eligibility criteria and data collection

All studies presenting original data that reported a rate of FALS (ie, the proportion of familial cases within a defined cohort) were included in the systematic review. Only studies that demonstrated complete enrolment, either in the form of population based registry or in sequential case series, were analysed. Studies with non-random enrolment or cohorts enriched for familial disease were not included in analysis.

Studies fulfilling inclusion criteria were grouped together according to the type of data presented: (1) prospective registry based studies that aim to capture all cases within a given geographic region in order to define incidence and prevalence; (2) retrospective studies that attempt to capture all cases in a given geographic region with the aim of estimating incidence and prevalence; (3) prospective cases series; and (4) retrospective case series.

**Table 1** Comparison of the type of study, rate of familial amyotrophic lateral sclerosis, source of case ascertainment and case inclusion criteria for each study

| Country | Years | FALS | Total ALS | % FALS | Ascertainment | Diagnosis | Comments |
|---|---|---|---|---|---|---|---|
| Group 1: prospective population based registry | | | | | | | |
| Puglia, Southern Italy | 1998–1999 | 2 | 130 | 1.50 | A, B, C, D, G, K | Bii, H, J, L, N | |
| Piemonte, Northern Italy | 1995–2004 | 53 | 1260 | 4.20 | A, D, H | Bii, N | |
| Scotland | 1989–1998 | 59 | 1226 | 4.80 | A, B, D, G, H, J | B, C | |
| South-East England | 2002–2006 | 31 | 472 | 6.60 | A, B, C, G, J | Bii, H | |
| Washington, USA | 1990–1994 | 9 | 174 | 5.20 | B, G | G, H, K, L | Personal communication with author |
| San Francisco, USA | 1970–1986 | 52 | 708 | 7.30 | A, B, C, G, H, L | A, D, H, J, N | Only paper to give criteria for familial ALS |
| Uruguay | 2002–2003 | 6 | 143 | 4.20 | A, B, H, J | Bi, I, K, M | States based on detailed family history |
| Ireland | 1995–2009 | 53 | 1170 | 4.50 | A, B, C, G, H, L | Bii, N | Up to date registry data (November 2009) |
| Group 2: retrospective population based study | | | | | | | |
| New Zealand | 1985–2006 | 10 | 244 | 4.10 | B, C, D, L | Bi, G, I, K | |
| Rochester, USA | 1925–1998 | 3 | 77 | 3.90 | E | P | |
| Modena, Italy | 1990–1999 | 4 | 143 | 2.80 | C, H, J, L | Bi | |
| Jefferson County, USA | 1998–2002 | 2 | 36 | 5.50 | B, C, D, G, H, I | Bi, I, M | Prevalence study looking for cluster |
| Ontario, Canada | 1978–1982 | 6 | 139 | 4.30 | C, G, H | D, H, K, L | |
| Middle Finland | 1976–1981 | 5 | 43 | 11.60 | D, H | D, O | |
| Northern Sweden | 1969–1980 | 6 | 128 | 4.70 | E, H, M | A, D, O | States that 4.7% should be taken as a minimum value |
| Cantabria, Spain | 1974–1985 | 3 | 65 | 4.60 | E | D, H, I | Poor case ascertainment |
| Sardinia, Italy | 1957–1980 | 4 | 182 | 2.20 | C | D | Poor case ascertainment. FALS limited to first degree relative |
| South-West Greece | 1990–2003 | 2 | 133 | 1.50 | E | Bi, F, I, N | |
| Belgrade, Yugoslavia | 1985–1991 | 1 | 58 | 1.70 | C | D, N | Poor ascertainment |
| Hong Kong | 1989–1992 | 1 | 84 | 1.20 | B, C, L, H | Bi, F, H, J, L, N | |
| Northern Denmark | 1974–1986 | 5 | 186 | 2.70 | C | D, O | |
| Hordaland, Norway | 1970–1990 | 7 | 148 | 4.70 | E, F, H | D, O | |
| Group 3: prospective case series | | | | | | | |
| Texas, USA | 1982–1994 | 114 | 1200 | 9.50 | E | E, N | States that data interpretation must be made in light of non-random enrolment |
| New York, USA | 1973–1977 | 33 | 668 | 4.90 | M | D | |
| Colorado, USA | 1989–1991 | 4 | 167 | 2.40 | C | D, E, N | |
| Group 4: retrospective case series | | | | | | | |
| Brazil | 1977–2004 | 7 | 251 | 2.80 | E | Bii, G, I, K, N | |
| London, UK | 1965–1984 | 27 | 580 | 4.70 | C | D | Case notes from 3 London hospitals. 37 FALS cases not verified—rate could be 10% |
| Rochester, USA | Pre 1955 | 5 | 58 | 9 | E | D | |
| Lazio, Italy | 1987–2007 | 23 | 531 | 4.30 | E | Bii, N | |
| Novia Scotia, Canada | Pre 1974 | 3 | 52 | 5.80 | E | D, F, H, J, L | |
| Leuven, Belgium | 1991–1995 | 12 | 140 | 8.60 | E | Bi, H, J, L | Especially high rate SOD1 mutation |
| Israel | 1959–1975 | 3 | 318 | 1 | C, I, M | C, D, E, N | |
| Netherlands | 1970–1988 | 20 | 307 | 6.50 | E | D, G, I, K | |

| Key | Ascertainment |
|---|---|
| A | Prospective register |
| B | All neurologists |
| C | Multicentre hospital records |
| D | Multicentre discharge records |
| E | Single centre hospital records |
| F | Single centre discharge records |
| G | ALS association records |
| H | Death certificates |
| I | Compulsory reporting |
| J | EMG archives |
| K | Control drug registry |
| L | Private neurologists |
| M | Questionnaire |

| Key | Diagnostic criteria |
|---|---|
| A | Post mortem |
| B | El Escorial criteria |
| Bi | EEC definite, probable |
| Bii | EEC definite, probable, suspect |
| C | Simplified EFN criteria |
| D | Diagnosed by neurologist pre-criteria |
| E | ALS rated using institutions own scoring system |
| F | SMA included |
| G | SMA excluded |
| H | PMA included |
| I | PMA excluded |
| J | PLS included |
| K | PLS excluded |
| L | PSP included |
| M | PSP excluded |
| N | EMG >80% patients |
| O | EMG <80% patients |

ALS, amyotrophic lateral sclerosis; EEC, El Escorial criteria; FALS, familial amyotrophic lateral sclerosis; PMA, progressive muscular atrophy; PSP, progressive supranuclear palsy; SMA, spinal muscular atrophy; WFN, World Federation of Neurology.

### Statistical analysis

In each study the rate of FALS is reported as the number of familial cases among all cases of ALS. Statistical analysis was carried out to combine proportions using the Meta function of R (R Development Core Team (2009). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0 http://www.R-project.org/).

The inverse variance method was used to pool proportions. Both fixed and random effects models were estimated and 95% CIs were calculated.

## RESULTS

### Systematic review

Fifty-four epidemiological studies provided original information on cohorts of patients with ALS.[9 10 13–66] A rate of FALS was reported in 38 of these studies,[9 10 13–46 63–66] although in no case was FALS ascertainment the primary objective. Five studies were not included in the analysis.[9 10 63–65] Of these, two were undertaken to genotype mutations in the ALS population. Both studies exhibited enrolment bias.[9 10] Three studies reported data on more than one occasion[63–65] and therefore only the most recent study was included in the meta-analysis. Reports from geographical areas with high incidence clusters (Guam/Kii Peninsula of Japan) were excluded.[66]

Of the 33 studies analysed,[13–46] eight reported incidence data from prospective population based registers[13–21]; 14 reported retrospective incidence and prevalence data[22–35]; three reported data from prospective case series of disease progression[44–46]; and eight reported data from retrospective case series.[36–43] Only two studies stated how they defined FALS.[30 44] In total, 575 cases of FALS were recorded among 11 221 reported cases of ALS.

The type of study, rate of FALS, source of case ascertainment and case inclusion criteria are outlined in table 1.[13–46]

### Meta-analysis

Pooled analysis of all studies generated a rate of FALS of 4.6% (95% CI 3.9% to 5.5%) (table 2).

A degree of heterogeneity was noted between reported rates of FALS in the prospective population based registers available for analysis.[13–21] The pooled result for rate of FALS for these studies was 5.1% (95% CI 4.1% to 6.1%).

In the 14 retrospective population based studies, the pooled result for rate of FALS was 3.7% (95% CI 2.9% to 4.7%)[22–36]

Figure 1 demonstrates a Forrest plot of the results.

The individual rate of FALS for each country in Europe was plotted on a map to determine a possible geographic pattern (figure 2).

Regions of relatively homogenous genetic origin, such as Ireland and Scotland (both of which both have large prospective databases of over 1200 patients) exhibit almost the same rate of FALS. Lower rates are reported in the more diverse populations of southern Italy and the Balkan Peninsula. Variations in the distribution of families with SOD1 mutations have also been identified. The population based rate of SOD1 mutations in Italian FALS patients is 13%, and the rate in sporadic ALS in 0.7%.[11] This contrasts sharply with rates of 1.9% in a Dutch FALS group and 0.44% in Dutch sporadic ALS patients.[67] The true population based rate of SOD1 gene mutations in other countries remains unclear, as the majority of studies performed to date have been neither prospective nor population based. Moreover, we were unable to identify a geographic correlation between FALS rates and reported SOD1 mutation rates for the same region.

## DISCUSSION

Our analysis indicates that the commonly accepted frequency of 10% for FALS represents an overestimation of the dominantly inherited Mendelian form of ALS. The population based frequency of 5.1% is likely to represent the most accurate estimation of rate of FALS, as population based studies include all patients in a defined geographic area in a given period of time. Accordingly, reported rates of FALS of 10% from previous studies are likely to have been biased by ascertainment from populations enriched by FALS cases.

Geographic variation in the rate of FALS in Europe (figure 2) may reflect true population based differences across different regions. Heterogeneity in the genetic substructure of European populations has been demonstrated recently.[68] These geographic differences may occur because of variability in the underlying genetic structure of the European population. However, difficulties in case ascertainment could also account for this difference. Evidence for population based differences is emerging for SOD1: a founder effect for the A4V mutations in SOD1 has been recently identified in the USA[69] and this mutation is rare in Europe. Mutations in OPTN seem to be primarily in Japanese populations.[70] The existence of geographic variability for TARDP and FUS has not yet been established. As more causative genes are identified in FALS, detailed analysis of the frequency of various mutations within individual FALS populations will become available.

The meta-analysis is limited by the absence of a clear definition of FALS. While most groups define FALS as the presence of ALS in at least two members of an extended kindred, the degree or relatedness and the size of the extended kindred are rarely considered. Given that the lifetime risk of ALS is 1:450 for women and 1:350 for men,[54 54a] there is an increasing probability of two affected members with sporadic ALS occurring in the same kindred as the size of the kindred increases. Therefore, ensuring segregation of mutations within kindreds is also

**Table 2** Meta-analysis results: subgroup analysis and pooled analysis

| | Proportion FALS cases (95% CI) | | | | | |
|---|---|---|---|---|---|---|
| **Study type** | **No of studies** | **FALS cases** | **Total ALS cases** | **Fixed effects** | **Random effects** | **$I^2$** |
| Group 1: prospective population based registry | 8 | 265 | 5283 | 5.0% (4.4 to 5.6) | 5.1% (4.1 to 6.1) | 56% |
| Group 2: retrospective population based study | 14 | 59 | 1666 | 3.7% (2.9 to 4.7) | 3.7% (2.9 to 4.7) | 0% |
| Group 3: prospective case series | 3 | 151 | 2035 | 7.3% (6.2 to 8.4) | 5.7% (2.5 to 9.9) | 91% |
| Group 4: retrospective case series | 8 | 100 | 2237 | 4.4% (3.6 to 5.2) | 4.8% (3.1 to 6.8) | 74% |
| Population based studies (groups 1 and 2) | 22 | 324 | 6949 | 4.7% (4.2 to 5.2) | 4.5% (3.8 to 5.3) | 37% |
| Case series studies (groups 3 and 4) | 11 | 251 | 4272 | 5.7% (5.0 to 6.4) | 5.1% (3.4 to 7.1) | 85% |
| Pooled results for all studies (groups 1–4) | 33 | 575 | 11,221 | 5.1% (4.7 to 5.5) | 4.6% (3.9 to 5.5) | 69% |

FALS, familial amyotrophic lateral sclerosis.

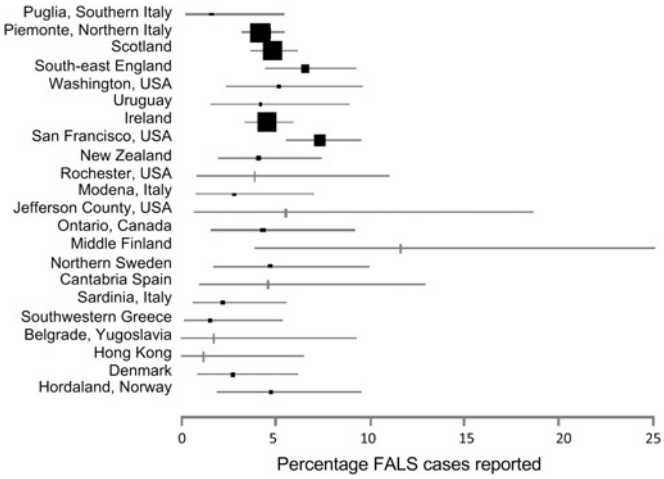


**Figure 1** Forrest plot of population based prospective and retrospective studies included in pooled analysis yielding a FALS rate of 4.5% (95% CI 3.8 to 5.3). FALS, familial amyotrophic lateral sclerosis.

important, as exemplified by a recent report of two apparent SOD1 kindreds in which the disease did not segregate with a known pathogenic SOD1 mutations.[71]

In conclusion, we have demonstrated that the rate of FALS across population based studies rarely exceeds 5% of all cases of ALS. This contrasts with the generally accepted figure of 10%, which originates from a paper written in 1955.[2]

Careful prospective population based analysis of kindreds using validated criteria for a diagnosis of FALS is required to confirm that 5% represents the true population based rate of familial ALS, and to determine whether the documented geographic variation in rates of FALS is corroborated.


**Figure 2** Rate of familial amyotrophic lateral sclerosis in individual European countries.

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## REFERENCES

1. **Wechsler IS,** Sapirstein MR, Stein A. Primary and symptomatic amyotrophic lateral sclerosis: a clinical study of 81 cases. *Am J Med Sci* 1944;**208**:70.
2. **Kurland L,** Mulder D. Epidemiologic investigations of amyotrophic lateral sclerosis. familial aggregation indicative of dominant inheritance Part I. *Neurology* 1955;**5**:182—96.
3. **Fang F,** Kamel F, Lichtenstein P, *et al*. Familial aggregation of amyotrophic lateral sclerosis. *Ann Neurol* 2009;**66**:94—9.
4. **Brown R.** Amyotrophic lateral sclerosis—insights from genetics. *Arch Neurol* 1997;**54**:1246—50.
5. **Valdmanis P,** Rouleau G. Genetics of familial amyotrophic lateral sclerosis. *Neurology* 2008;**70**:144—52.
6. **Majoor-Krakauer D,** Willems PJ, Hofman A. Genetic epidemiology of amyotrophic lateral sclerosis. *Clin Genet* 2003;**63**:83—101.
7. **Shaw PJ.** Genetic inroads in familial ALS. *Nat Genet* 2003;**29**:103—4.
8. **Andersen PM,** Borasio GD, Dengler R, *et al*. Good practice in the management of amyotrophic lateral sclerosis: clinical guidelines. An evidence-based review with good practice points. EALSC Working Group. *Amyotroph Lateral Scler* 2007;**8**:195—213.
9. **Andersen PM,** Nilsson P, Keränen ML, *et al*. Phenotypic heterogeneity in motor neuron disease patients with CuZn-superoxide dismutase mutations in Scandinavia. *Brain* 1997;**120**:1723—37.
10. **Eisen A,** Mezei M, Stewart H, *et al*. SOD1 gene mutations in ALS patients from British Columbia, Canada: Clinical features, neurophysiology and ethical issues in management. *Amyotroph Lateral Scler* 2008;**9**:108—19.
11. **Chio A,** Traynor BJ, Lombardo F, *et al*. Prevalence of SOD1 mutations in the Italian ALS population. *Neurology* 2008;**70**:533—7.
12. **Orwell RW,** Habgood JJ, Malaspina A, *et al*. Clinical characteristics of SOD1 gene mutation in UK families with ALS. *J Neurol Sci* 1999;**169**:56—60.
13. **Logroscino G,** Beghi E, Zoccolella S, *et al*. Incidence of amyotrophic lateral sclerosis in southern Italy: a population based study. *J Neurol Neurosurg Psychiatry* 2005;**76**:1094—8.
14. **Chiò A,** Mora G, Calvo A, *et al*. Epidemiology of ALS in Italy. A 10-year prospective population-based study. *Neurology* 2009;**72**:725—31.
15. **Forbes R,** Colville S, Parratt J, *et al*. The incidence of motor neuron disease in Scotland. *J Neurol* 2007;**254**:866—9.
16. **Abhinav K,** Stanton B, Johnston C, *et al*. Amyotrophic lateral sclerosis in South-East England: a population-based study. The South-East England register for amyotrophic lateral sclerosis (SEALS Registry). *Neuroepidemiology* 2007;**29**:44—8.
17. **McGuire V,** Longstreth WT, Koepsell T, *et al*. Incidence of amyotrophic lateral sclerosis in three counties in western Washington State. *Neurology* 1996;**47**:571—3.
18. **del Aguila MA,** Longstreth WT, Koepsell T, *et al*. Prognosis in amyotrophic lateral sclerosis: a population-based study. *Neurology* 2003;**60**:813—19.
19. **Cruz DC,** Nelson LM, McGuire V, *et al*. Physical trauma and family history of neurodegenerative diseases in amyotrophic lateral sclerosis: a population-based case-control study. *Neuroepidemiology* 1999;**18**:101—10.
20. **Vzquez MC,** Ketzoian C, Legnani C, *et al*. Incidence and prevalence of amyotrophic lateral sclerosis in Uruguay: a population-based study. *Neuroepidemiology* 2008;**30**:105—11.
21. **Norris F,** Shepherd R, Denys E, *et al*. Onset, natural history and outcome in idiopathic adult motor neuron disease. *J Neurol Sci* 1993;**118**:48—55.
22. **Murphy M,** Quinn S, Young J, *et al*. Increasing incidence of ALS in Canterbury, New Zealand: A 22-year study. *Neurology* 2008;**71**:1889—95.
23. **Sorenson EJ,** Stalker AP, Kurland L, *et al*. Amyotrophic lateral sclerosis in Olmsted County, Minnesota, 1925 to 1998. *Neurology* 2002;**59**:280—2.
24. **Mandrioli J,** Faglioni P, Merelli E, *et al*. The epidemiology of ALS in Modena, Italy. *Neurology* 2003;**60**:683—9.
25. **Turabelidze G,** Zhu BP, Schootman M, *et al*. An epidemiologic investigation of amyotrophic lateral sclerosis in Jefferson County, Missouri, 1998—2002. *Neurotoxicology* 2008;**29**:81—6.
26. **Hudson AJ,** Davenport A, Hader WJ. The incidence of amyotrophic lateral sclerosis in southwestern Ontario, Canada. *Neurology* 1986;**36**:1524.
27. **Murros K,** Fogelholm R. Amyotrophic lateral sclerosis in Middle-Finland: an epidemiological study. *Acta Neurol Scand* 1983;**67**:41—7.
28. **Forsgren L,** Almay B, Holmgren G, *et al*. Epidemilogy of motor neuron disease in northern Sweden. *Acta Neurol Scand* 1983;**68**:20—9.
29. **Lopez-Vega JM,** Calleja J, Combarros O, *et al*. Motor neuron disease in Cantabria. *Acta Neurol Scand* 1988;**77**:1—5.
30. **Giaggheddu M,** Puggioni G, Masala C, *et al*. Epidemiologic study of amyotrophic lateral sclerosis in Sardinia, Italy. *Acta Neurol Scand* 1983;**68**:394—404.
31. **Argyriou AA,** Polychronopoulos P, Papapetropoulos S, *et al*. Clinical and epidemiological features of motor neuron disease in south-western Greece. *Acta Neurol Scand* 2005;**111**:108—13.

32. **Alcaz S,** Jarwbincki M, Pekmezovic T, *et al*. Epidemiological and clinical characteristics of ALS in Belgrade, Yugoslavia. *Acta Neurol Scand* 1996;**94**:264—8.
33. **Fong KY,** Yu YL, Chan YW, *et al*. Motor neuron disease in Hong Kong Chinese: epidemiology and clinical picture. *Neuroepidemiology* 1996;**15**:239—45.
34. **Hojer-Pedersen E,** Christensen PB, Jensen NB. Incidence of prevalence of motor neuron disease in two Danish counties. *Neuroepidemiology* 1989;**8**:151—9.
35. **Tysnes OB,** Vollset SE, Aarli JA. Epidemiology of amyotrophic lateral sclerosis in Hordaland county, western Norway. *Acta Neurol Scand* 1991;**83**:280—5.
36. **Werneck LC,** Bezerra R, Silveira O, *et al*. A clinical epidemiological study of 251 cases of amyotrophic lateral sclerosis in the south of Brazil. *Arq Neuropsiquiatr* 2007;**65**:189—95.
37. **Li TM,** Alberman E, Swash M. Comparison of sporadic and familial disease amongst 580 cases of motor neuron disease. *J Neurol Neurosurg Psychiatry* 1988;**51**:778—84.
38. **Kurland L,** Mulder D. Epidemiologic investigations of amyotrophic lateral sclerosis. Familial aggregation indicative of dominant inheritance part II. *Neurology* 1955;**5**:249—68.
39. **Sabatelli M,** Madia F, Conte A, *et al*. Natural history of young-adult amyotrophic lateral sclerosis. *Neurology* 2008;**71**:876—81.
40. **Murray TJ,** Pride S, Haley G. Motor neuron disease in Novia Scotia. *Can Med Assoc J* 1974;**110**:814—17.
41. **Thjis V,** Peeters E, Theys P, *et al*. Demographic characteristics and prognosis in a Flemish amyotrophic lateral sclerosis population. *Acta Neurol Belg* 2000;**100**:84—90.
42. **Gubbay S,** Kahana E, Zilber N, *et al*. Amyotrophic lateral sclerosis. A study of its presentation and prognosis. *J Neurol* 1985;**232**:295—300.
43. **Louwerse ES,** Visser CE, Bossuyt PM, *et al*. Amyotrophic lateral sclerosis: mortality risk during the course of the disease and prognostic factors. *J Neurol Sci* 1997;**152**(Suppl 1):10—17.
44. **Haverkamp LJ,** Appel V, Appel SH. Natural history of amyotrophic lateral sclerosis in a database population: Validation of a scoring system and a model for survival prediction. *Brain* 1995;**3**:118.
45. **Rosen A.** Amyotrophic lateral sclerosis: clinical features and prognosis. *Arch Neurol* 1978;**35**:638—42.
46. **Ringel SP,** Murphy JR, Alderson MK, *et al*. The natural history of amyotrophic lateral sclerosis. *Neurology* 1993;**43**:1316—21.
47. **Fang F,** Valdimarsdottir U, Bellocco R, *et al*. Amyotrophic lateral sclerosis in Sweden, 1991—2005. *Arch Neurol* 2009;**66**:515—19.
48. **Marin B,** Gil J, Preux PM, *et al*. Incidence of amyotrophic lateral sclerosis in the Limousin region of France, 1997—2007. *Amyotroph Lateral Scler* 2009;**10**:216—20.
49. **Beghi E,** Millil A, Micheli A, *et al*. Incidence of ALS in Lombardy, Italy. *Neurology* 2007;**68**:141—5.
50. **Zaldivar T,** Gutierrez J, Lara G, *et al*. Reduced frequency of ALS in an ethnically mixed population: A population-based mortality study. *Neurology* 2009;**72**:1640—5.
51. **Fong GC,** Cheng TS, Lam K, *et al*. An epidemiological study of motor neuron disease in Hong Kong. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2005;**6**:164—8.
52. **Gil J,** Vazquez MC, Ketzoian C, *et al*. Prognosis of ALS: Comparing data from the Limousin referral centre, France, and a Uruguayan population. *Amyotroph Lateral Scler* 2009;**10**:355—60.
53. **Nalini A,** Thennarasu K, Gourie-Devi M, *et al*. Clinical characteristics and survival pattern of 1153 patients with amyotrophic lateral sclerosis: Experience over 30 years from India. *J Neurol Sci* 2008;**272**:60—70.
54. **Alonso A,** Logroscino G, Jick SS, *et al*. Incidence and lifetime risk of motor neuron disease in the United Kingdom: a population-based study. *Eur J Neurol* 2009;**16**:745—51.

54a. **Johnston CA,** Stanton BR, Turner MR, *et al*. Amyotrophic lateral sclerosis in an urban setting. A population based study of inner city London. *J Neurol* 2006;**252**:1642—3.

55. **Kahana E,** Alter M, Feldman M. Amyotrophic lateral sclerosis—a population Study. *J Neurol* 1976;**212**:205—13.
56. **Okamoto K,** Kobashi G, Washio M, *et al*. Descriptive epidemiology of amyotrophic lateral sclerosis in Japan, 1995—2001. *J Epidemiol* 2005;**15**:20—3.
57. **Mulder DW,** Kurland LT, Offord KP, *et al*. Familial motor neuron disease: amyotrophic lateral sclerosis. *Neurology* 1986;**36**:511—17.
58. **Chiò A,** Magnani C, Schiffer D. Amyotrophic lateral sclerosis mortality in Italy, 1958 to 1987. A cross-sectional and cohort study. *Neurology* 1993;**43**:927.
59. **Matsumoto N,** Worth R, Kurland L, *et al*. Epidemiologic study of ALS in Hawaii. *Neurology* 1972;**22**:934—40.
60. **Juergens S,** Kurland L, Okazaki H, *et al*. ALS in Rochester, Minnesota, 1925—1977. *Neurology* 1980;**30**:463.
61. **Neilson S,** Gunnarsson LG, Robinson I, *et al*. Rising mortality in motor neuron disease in Sweden 1961—1990. *Acta Neurol Scand* 1994;**90**:150—9.
62. **Giagheddu M,** Mascia V, Cannas A, *et al*. Amyotrophic lateral sclerosis in Sardinia Italy; an epidemiological study. *Acta Neurol Scand* 1993;**87**:446—54.
63. **O'Toole O,** Traynor BJ, Brennan P, *et al*. Epidemiology and clinical features of amyotrophic lateral sclerosis in Ireland between 1995 and 2004. *J Neurol Neurosurg Psychiatry* 2008;**79**:30—2.
64. **Zoccolella S,** Beghi E, Palagano G, *et al*. Signs and symptoms at diagnosis of amyotrophic lateral sclerosis: a population-based study in southern Italy. *Eur J Neurol* 2006;**13**:789—92.
65. **The Scottish Motor Neuron Disease Research Group.** The Scottish Motor Neuron Disease Register: a prospective study of adult onset motor neuron disease in Scotland. Methodology, demography and clinical features of incident cases in 1989. *J Neurol Neurosurg Psychiatry* 1992;**55**:536—41.
66. **Kihira T,** Yoshida S, Hironishi M, *et al*. Changes in the incidence of amyotrophic lateral sclerosis in Wakayama, Japan. *Amyotroph Lateral Scler* 2005;**6**:155—63.
67. **van Es MA,** Dahlberg C, Birve A, *et al*. Large scale SOD1 mutation screening provides evidence for genetic heterogeneity in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 2010;**81**:562—6.
68. **Novembre J,** Johnson T, Bryc K, *et al*. Genes mirror geography within Europe. *Nature* 2008;**456**:98—101.
69. **Saeed M,** Yang Y, Deng H-X, *et al*. Age and founder effect of SOD1 A4V mutation causing ALS. *Neurology* 2009;**72**:1634—9.
70. **Maruyama H,** Morino H, Ito H, *et al*. Mutations of optineurin in amyotrophic lateral sclerosis. *Nature* 2010;**465**:223—6.
71. **Rabe M,** Felbecker A, Waibel S, *et al*. The epidemiology of CuZn-SOD mutations in Germany: a study of 217 families. *J Neurol* 2010;**257**:1298—302.