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Title Page

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: Thirty-eight 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 3.9-5.5). Restricting the analysis to prospective population-based registry data revealed a rate of 5.1% (95% CI 4.1-6.1). 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 4.1-6.1%), 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 ALS². Although subsequent publications have reported varying rates of FALS, the figure of 10% remains as the accepted population frequency of FALS³⁻⁷.

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 ANG⁸. The frequency of SOD1 mutations has been estimated to account for 10-20% of all FALS cases⁶. 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 penetrance¹². 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 present original data reporting a rate of FALS (i.e. the proportion of familial cases amongst 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 (i.e. the proportion of familial cases within a defined cohort) were included in the systematic review. Only studies that demonstrated complete enrollment, either in the form of population-based registry or in sequential case series, were analysed. Studies with non-random enrollment 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, 4) Retrospective case series.

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, URL <http://www.R-project.org>.*)

The inverse variance method was used to pool proportions. Both Fixed and Random effects models were estimated and confidence intervals of 95% were calculated.

Results

Systematic review: Fifty four epidemiologic 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 analysis^{9,10,63-65}. Of these, two were undertaken to genotype mutations in the ALS population. Both studies exhibited enrollment bias^{9,10}. Three studies reported data on more than one occasion⁶³⁻⁶⁵ 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 excluded⁶⁶.

Of the thirty-three studies analysed¹³⁻⁴⁶, 8 reported incidence data from prospective population-based registers¹³⁻²¹; 14 reported retrospective incidence and prevalence data; ²²⁻³⁵, 3 reported data from prospective case series of disease progression⁴⁴⁻⁴⁶ and 8 reported data from retrospective case series³⁶⁻⁴³. 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

Table 1. Comparison of the type of study, rate of FALS, 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 enrollment.
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			Key	Diagnostic Criteria		
A	Prospective Register			A	Post mortem		
B	All neurologists			B	El Escorial Criteria		
C	Multi-centre hospital records			Bi	EEC Definite, Probable.		
D	Multi-centre discharge records			Bii	EEC Definite, Probable, Suspect.		
E	Single centre hospital records			C	Simplified EFN criteria		
F	Single centre discharge records			D	Diagnosed by Neurologist pre-criteria		
G	ALS association records			E	ALS rated using institutions own scoring system		
H	Death certificates			F	SMA included		
I	Compulsory reporting			G	SMA excluded		
J	EMG archives			H	PMA included		
K	Control drug registry			I	PMA excluded		
L	Private neurologists			J	PLS included		
M	Questionnaire			K	PLS excluded		
				L	PSP included		
				M	PSP excluded		
				N	EMG > 80% patients		
				O	EMG < 80% patients		

Meta-Analysis

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

Table 2. Meta-analysis results: Subgroup analysis and pooled analysis

Study Type	Number of studies	FALS cases	Total ALS cases	Proportion FALS cases (95% CI)		I ²
				Fixed Effects	Random Effects	
Group 1 - Prospective Population based registry	8	265	5283	5.0% (4.4-5.6)	5.1% (4.1-6.1)	56%
Group 2 - Retrospective Population based study	14	59	1666	3.7% (2.9-4.7)	3.7% (2.9-4.7)	0%
Group 3- Prospective case series	3	151	2035	7.3% (6.2-8.4)	5.7% (2.5-9.9)	91%
Group 4 - Retrospective case series	8	100	2237	4.4% (3.6-5.2)	4.8% (3.1-6.8)	74%
Population based studies (Group 1 and 2)	22	324	6949	4.7% (4.2-5.2)	4.5% (3.8-5.3)	37%
Case series studies (Group 3 and 4)	11	251	4272	5.7% (5.0-6.4)	5.1% (3.4-7.1)	85%
Pooled results for all studies (Groups 1,2,3,4)	33	575	11,221	5.1% (4.7-5.5)	4.6% (3.9-5.5)	69%

A degree of heterogeneity was noted between reported rates of FALS in the prospective population based registers available for analysis¹³⁻²¹. The pooled result for rate of FALS for these studies was 5.1% (95% CI 4.1-6.1).

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

Figure 1 demonstrates a Forrest plot of the results (see figure 1).

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

Regions of relatively homogenous genetic origin, such as Ireland and Scotland, (both of which both have large prospective databases of over twelve hundred 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 SALS is 0.7%¹¹. This contrasts sharply with rates of 1.9% in Dutch FALS group and 0.44% in Dutch SALS patients⁶⁷. 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 recently⁶⁸. 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 USA⁶⁹ and this mutation is rare in Europe. Mutations in OPTN seem to be primarily in Japanese populations⁷⁰. 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 of relatedness and the size of the extended kindred are rarely considered. Given that the lifetime risk of ALS is 1:450 for females and 1:350 for males⁷¹, there is an increasing probability of 2 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 important, as exemplified by a recent report of two apparent SOD1 kindreds in which the disease did not segregate with a known pathogenic SOD1 mutations⁷².

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 1955².

Careful prospective population based analysis of kindreds using validated criteria for 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.

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References

1. Wechsler I S, Sapirstein M R, Stein A. Primary and symptomatic Amyotrophic Lateral Sclerosis: A clinical study of 81 cases. *Am. J. Med. Sc.* 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: 182-196
3. F Fang, F Kamel, P Lichtenstein et al. Familial Aggregation of Amyotrophic Lateral Sclerosis. *Ann Neurol* 2009;66: 94-99
4. Brown R. Amyotrophic Lateral Sclerosis – Insights from Genetics. *Arch Neurol* 1997;54: 1246-1250
5. Valdmanis P, Rouleau G. Genetics of Familial Amyotrophic Lateral Sclerosis. *Neurology* 2008; 70: 144-152
6. Majoor-Krakauer D, Willems P J, Hofman A. Genetic Epidemiology of Amyotrophic Lateral Sclerosis. *Clin Genet* 2003: 63: 83-101
7. Shaw P J. Genetic inroads in familial ALS. *Nature Genet.* 2003: 29: 103-104
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 Aug;8(4):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: 1723–1737
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. *Amyotrophic Lateral Sclerosis* 2008; 9: 108 — 119
11. Chio A, Traynor BJ, Lombardo F et al. Prevalence of SOD1 mutations in the Italian ALS population. *Neurol* 2008; 70; 533-537
12. Orwell RW, Habgood JJ, Malaspina A et al. Clinical characteristics of SOD1 gene mutation in UK families with ALS. *Journal of the Neurological Sciences* 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;76:1094-109
14. Chiò A, Mora G, Calvo A et al. Epidemiology of ALS in Italy A 10-year prospective population-based study. *Neurology* 2009;72:725-731
15. Forbes R, Colville S, Parratt J et al. The incidence of Motor Neuron Disease in Scotland. *J Neurol* 2007;254: 866-869
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). *Neuroepid* 2007;29:44–48
17. McGuire V, Longstreth WT, Koepsell T et al. Incidence of amyotrophic lateral sclerosis in three counties in western Washington state. *Neurology*.1996; 47: 571-573
18. del Aguila MA, Longstreth WT, Koepsell T et al. Prognosis in amyotrophic lateral

- sclerosis: A population-based study. *Neurology* 2003; 60: 813-819
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. *Neuroepid* 1999;18:101-110
20. Vazquez MC, Ketzoian C, Legnani C et al. Incidence and prevalence of Amyotrophic Lateral Sclerosis in Uruguay: a population-based study. *Neuroepid* 2008; 30: 105-111
21. Norris F, Shepherd R, Denys E et al. Onset, natural history and outcome in idiopathic adult motor neuron disease. *Journal of the Neurological Sciences* 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;1889-1895
23. Sorenson EJ, Stalker AP, Kurland L et al. Amyotrophic lateral sclerosis in Olmsted County, Minnesota, 1925 to 1998. *Neurology*.2002; 59: 280-282
24. Mandrioli J, Faglioni P, Merelli E et al. The epidemiology of ALS in Modena, Italy. *Neurology*.2003; 60: 683-689
25. Turabelidze G, Bao-Ping Zhu , Schootman M et al. An epidemiologic investigation of amyotrophic lateral sclerosis in Jefferson County, Missouri, 1998-2002. *Neurotoxicology* 2008; 29: 81-86
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: 41-47
28. Forsgren L, Almay B, Holmgren G et al. Epidemiology of motor neuron disease in northern Sweden. *Acta Neurol Scand* 1983: 68: 20-29

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: 108–113
32. Alcaz S, Jarwbincki M, Pekmezovic T et al. Epidemiological and clinical characteristics of ALS in Belgrade, Yugoslavia. *Acta Neurol Scand* 1996; 94; 264-268
33. Fong KY, Yu YL, Chan YW et al. Motor Neuron Disease in Hong Kong Chinese: Epidemiology and Clinical Picture. *Neuroepid* 1996; 15; 239-245
34. Hojer-Pedersen E, Christensen PB, Jensen NB. Incidence of prevalence of Motor Neuron Disease in Two Danish Counties. *Neuroepid* 1989; 8; 151-159
35. Tysnes OB, Vollset SE, Aarli JA. Epidemiology of amyotrophic lateral sclerosis in Hordaland county, western Norway. *Acta Neurol Scand* 1991; 83: 280-285
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;65:189-195.
37. T M Li, E Alberman, M Swash. Comparison of sporadic and familial disease amongst 580 cases of motor neuron disease. *J Neurol Neurosurg Psychiatry* 1988;51:778-784

38. Kurland L, Mulder D. Epidemiologic Investigations of Amyotrophic Lateral Sclerosis. Familial Aggregation indicative of Dominant Inheritance. Part II
Neurology 1955;5: 249-268
39. Sabatelli M, Madia F, Conte A et al. Natural history of young-adult amyotrophic lateral sclerosis. *Neurology 2008; 71: 876-881*
40. Murray TJ, Pride S, Haley G. Motor Neuron Disease in Nova Scotia. *CMA Journal 1974: 110; 814-817*
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. *Journal of Neurology 1985: 232; 295-300*
43. Louwense ES, Visser CE, Bossuyt PM et al. Amyotrophic lateral sclerosis: mortality risk during the course of the disease and prognostic factors. *Journal of Neurological Sciences 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; Jun 1995; 3: 118*
45. Rosen A. Amyotrophic Lateral Sclerosis: Clinical features and prognosis. *Arch Neurol 1978: 35: 638-642*
46. Ringel SP, Alderson MK, Bryan W. The natural history of ALS. *Neurol 1993;43; 1316-1321*
47. Fang Fang, Valdimarsdottir U, Bellocco R et al. Amyotrophic Lateral Sclerosis in Sweden, 1991-2005. *Arch Neurol 2009: 66(4): 515-519*
48. Marin B, Gil J, Preux PM et al. Incidence of amyotrophic lateral sclerosis in the

- Limousin region of France, 1997-2007. *Amyotrophic Lateral Sclerosis* 2009 ;10: 216-220
49. Beghi E, Millil A, Micheli A et al. Incidence of ALS in Lombardy, Italy. *Neurology* 2007; 68: 141-145
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;1640-1645
51. Fong GCY, Cheng TS, Lam K et al. An epidemiological study of motor neuron disease in Hong Kong. *Amyotrophic Lateral Sclerosis* 2005; 6: 164-168
52. Gil J, Vazquez MC, Ketzoian C et al. Prognosis of ALS: Comparing data from the Limousin referral centre, France, and a Uruguayan population. *Amyotrophic Lateral Sclerosis* 2009 : May 22 Epub.
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 S et al. Incidence and lifetime risk of motor neuron disease in the United Kingdom: a population-based study. *Eur J Neurol* 2009: 16: 745-751
55. Kahana E, Alter M, Feldman M. Amyotrophic Lateral Sclerosis-A Population Study. *J Neurol* 1976: 212: 205-213
56. Okamoto K, Kobashi G, Washio M et al. Descriptive epidemiology of Amyotrophic Lateral Sclerosis in Japan, 1995-2001. *J Epid* 2005 :15: 20-23
57. Mulder DW, Kurland LT, Offord KP et al. Familial Motor Neuron Disease: Amyotrophic Lateral Sclerosis. *Neurology* 1986; 36: 511-517
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: 934-940
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: 150-159
62. Giagheddu M, Mascia V, Cannas A et al. Amyotrophic Lateral Sclerosis in Sardinia Italy; an epidemiological study. *Acta Neurol Scand* 1993 : 87: 446-454
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; 30-32
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: 789-792
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; 55:536-541
66. Kihira T, Yoshida S, Hironishi M et al. Changes in the incidence of Amyotrophic Lateral Sclerosis in Wakayama, Japan. *Amyotrophic Lateral Sclerosis* 2005: 6: 155-163
67. A van Es M, Dahlberg C, Birve A, et al. Large scale SOD1 mutation screening

- provides evidence for genetic heterogeneity in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* published online December 3, 2009
68. Novembre , 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. *Neurol* 2009; 72; 1634-1639
70. Maruyama H, Morino H, Ito H et al. Mutations of optineurin in amyotrophic lateral sclerosis. *Nature*. 2010 May 13;465(7295):223-6. Epub 2010 Apr 28.
71. Alonso A, Logroscino G, Jick SS et al. Incidence and lifetime risk of Motor Neuron Disease in the United Kingdom, a population based study. *European Journal of Neurology* 2009; 16 (6); 745-751
72. Rabe M, Felbecker A, Waibel S et al. The epidemiology of CuZn-SOD mutations in Germany: a study of 217 families. *J Neurol* 2010 DOI 10.1007/s00415-010-5512-9

Figure 1. Forrest Plot of population-based prospective and retrospective studies included in pooled analysis yielding FALS rate 4.5% (95% CI 3.8-5.3).

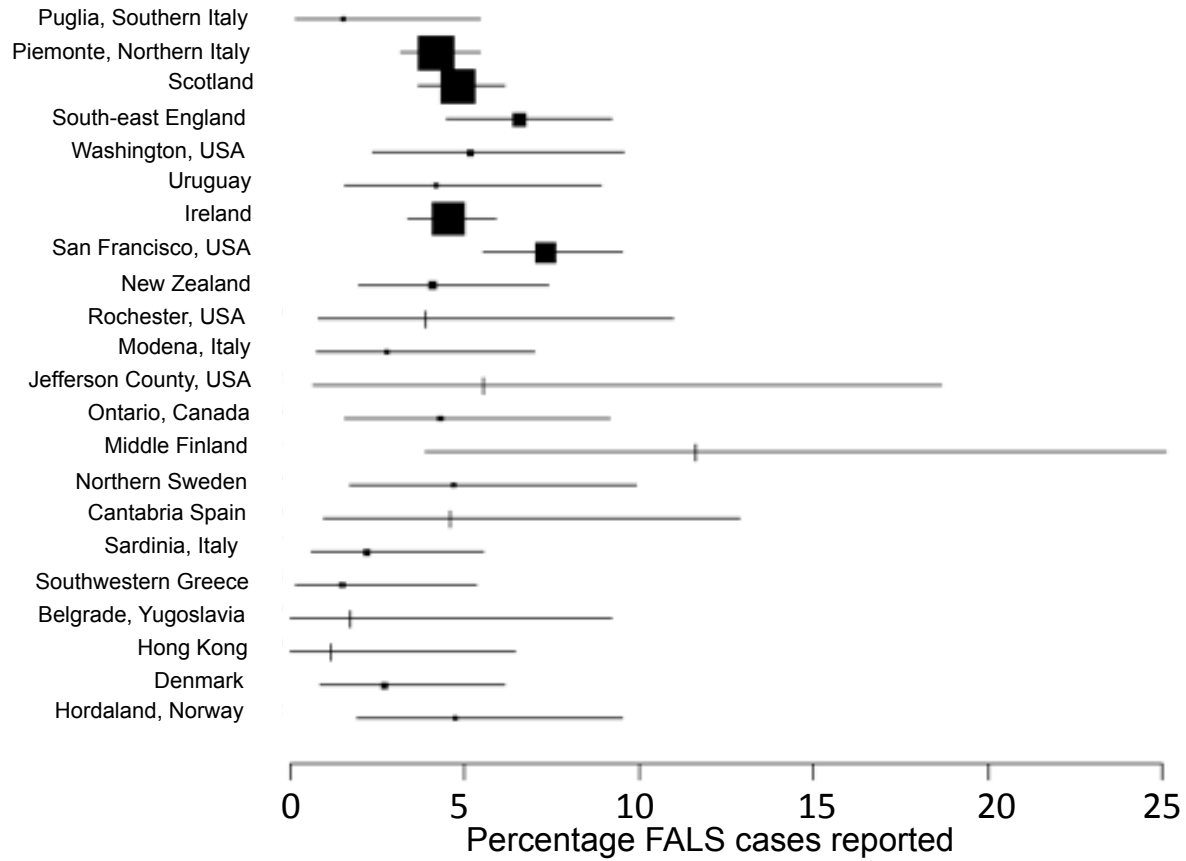


Figure 2. Rate of FALS in individual European countries

