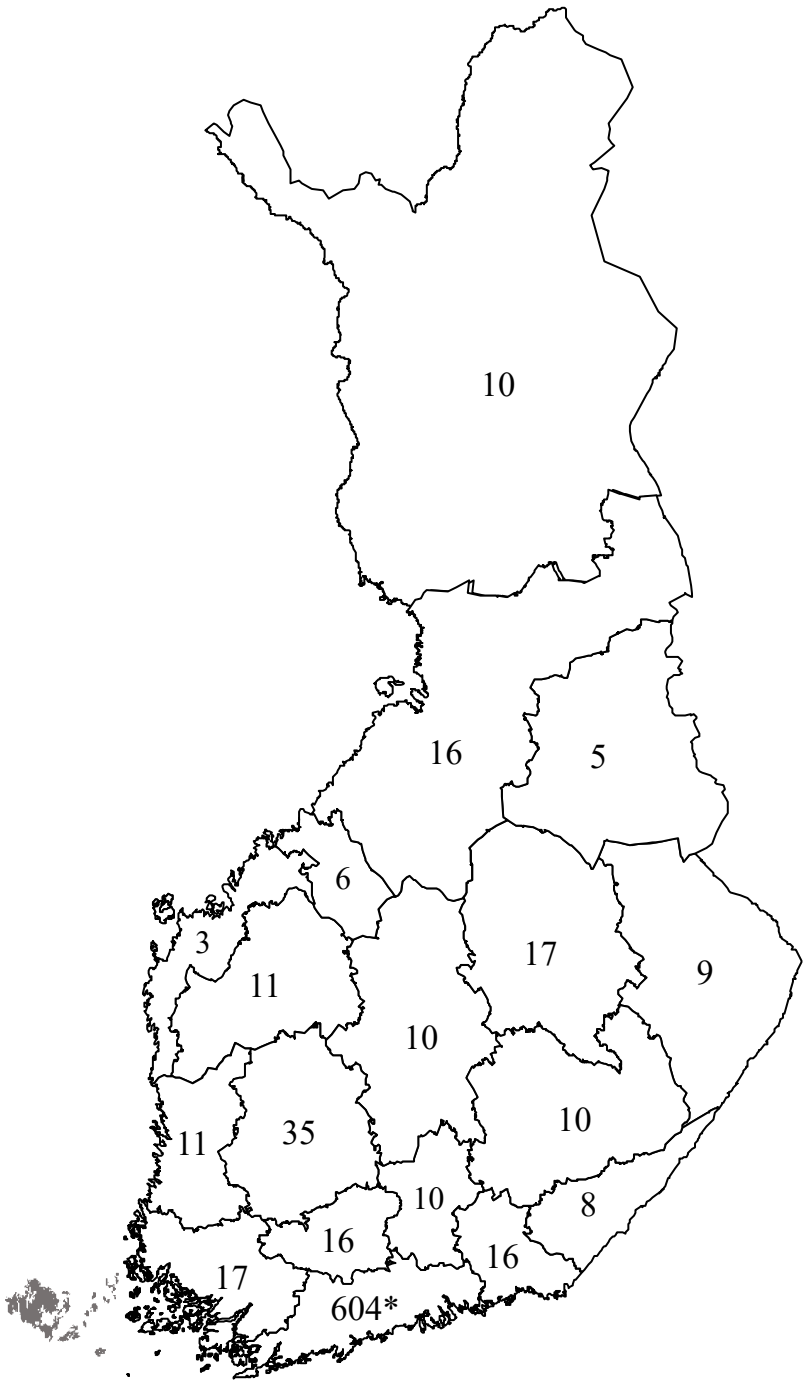
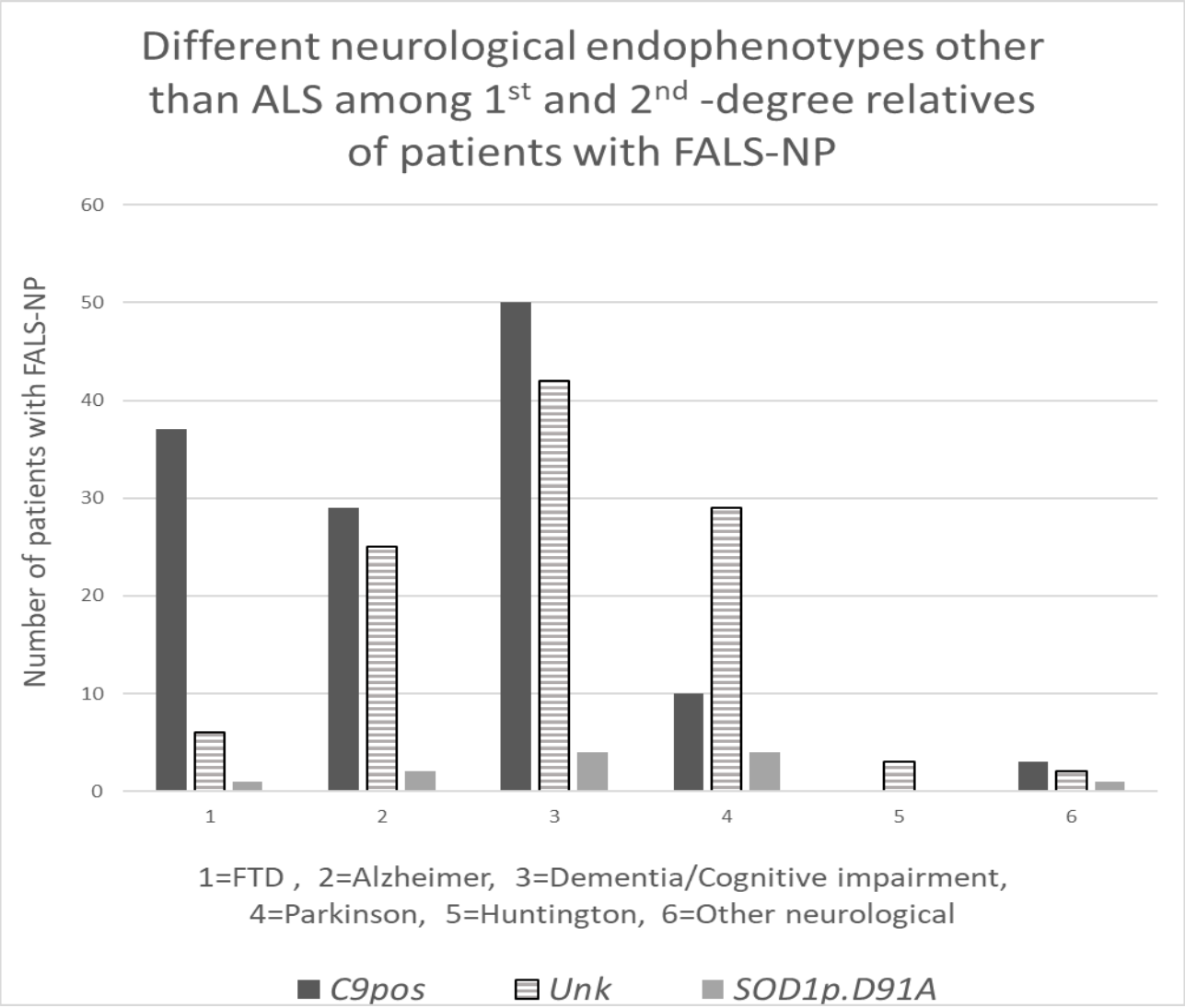
eFigure 1. Geographic distribution of Finnish ALS cases by domiciles (one patient lived abroad). The frequencies of the ALS cases with the *C9orf72* hexanucleotide repeat expansion (*C9pos*) as well as *SOD1*p.D91A (homozygotes) and *SOD1*p.A90V mutations among 815 patients from Uusimaa* and other regions shown above the map.

	Uusimaa* (n=604)	Other regions (n=211)	p-value
	n (%)	n (%)	(Fisher's exact test)
C9pos	183 (30,3%)	73 (34,6%)	0.26
*SOD1*p.D91A	33 (5.5%)	39 (18,5%)	1.3 x 10-7
*SOD1*p.A90V	4 (0.7%)	3 (1,4%)	0.38

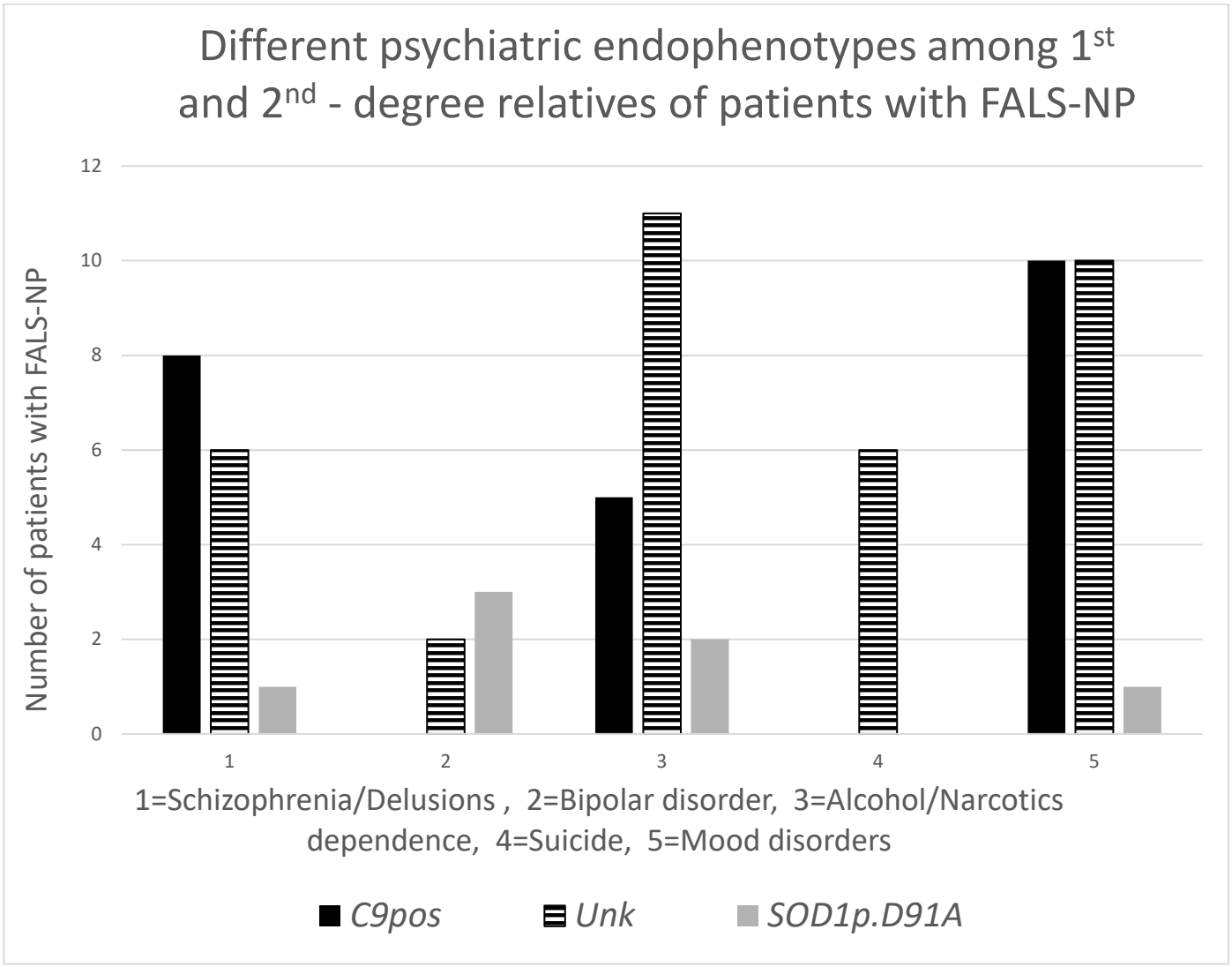


eFigure 2A. Neurological endophenotypes among relatives of patients with FALS-NP



eFigure 2A. Different neurological endophenotypes (1-6) other than ALS among 1st and 2nd -degree relatives of patients with FALS-NP. Each column represents the amount of different endophenotypes observed in the index patient´s family. Each unique endophenotype is counted only once per family and do not represent the total number of relatives affected. The group populations are: *C9pos* (n=256), *Unk* (n= 480), *SOD1*p.D91A (n=72).

eFigure 2B. Psychiatric endophenotypes among relatives of patients with FALS-NP



eFigure 2B. Different psychiatric endophenotypes (1-5) other than ALS among 1st and 2nd -degree relatives of patients with FALS-NP. Each column represents the amount of different endophenotypes observed in the index patient´s family. Each unique endophenotype is counted only once per family and do not represent the total number of relatives affected. The group populations are: *C9pos* (n=256), *Unk* (n= 480), *SOD1*p.D91A (n=72).

eTable1. Modifiers of age-of-onset according to sex, site-of-onset and the presence of the *C9orf72* hexanucleotide expansion (*C9pos*/*Unk*). *SOD1*p.D91A homozygotes and *SOD1*p.A90V heterozygotes were excluded.

	n	Median age-of-onset (range)	p
C9pos			
Bulbar vs.	89	59 yr (37-79)	0.048
Limb	163	57 yr (35-75)	
C9pos Bulbar			
Female vs.	50	60 (42-79)	0.20
Male	39	57 (37-76)	
C9pos Limb			
Female vs.	88	56.5 yr (39-74)	0.37
Male	75	57 yr (35-75)	
C9pos			
Female vs.	138	58 yr (39-79)	0.13
Male	114	57 yr (35-76)	
Unk			
Bulbar vs.	176	66 yr (38-88)	4.6×10^{-12}
Limb	279	57 yr (27-86)	
Unk Bulbar			
Female vs.	107	67 yr (38-88)	0.33
Male	69	65 yr (40-87)	
Unk Limb			
Female vs.	121	59 yr (27-86)	0.40
Male	158	58 yr (29-85)	
Unk			
Female vs.	228	62 yr (27-88)	0.018
Male	227	60 yr (29-87)	

C9pos = C9orf72 repeat expansion carrier, *Unk* = non-carrier, Bulbar = bulbar-onset, Limb = limb-onset.

<u>eFigure</u> 3. Cumulative incidence of ALS by age dichotomized by sex, familiality, and site-of-onset

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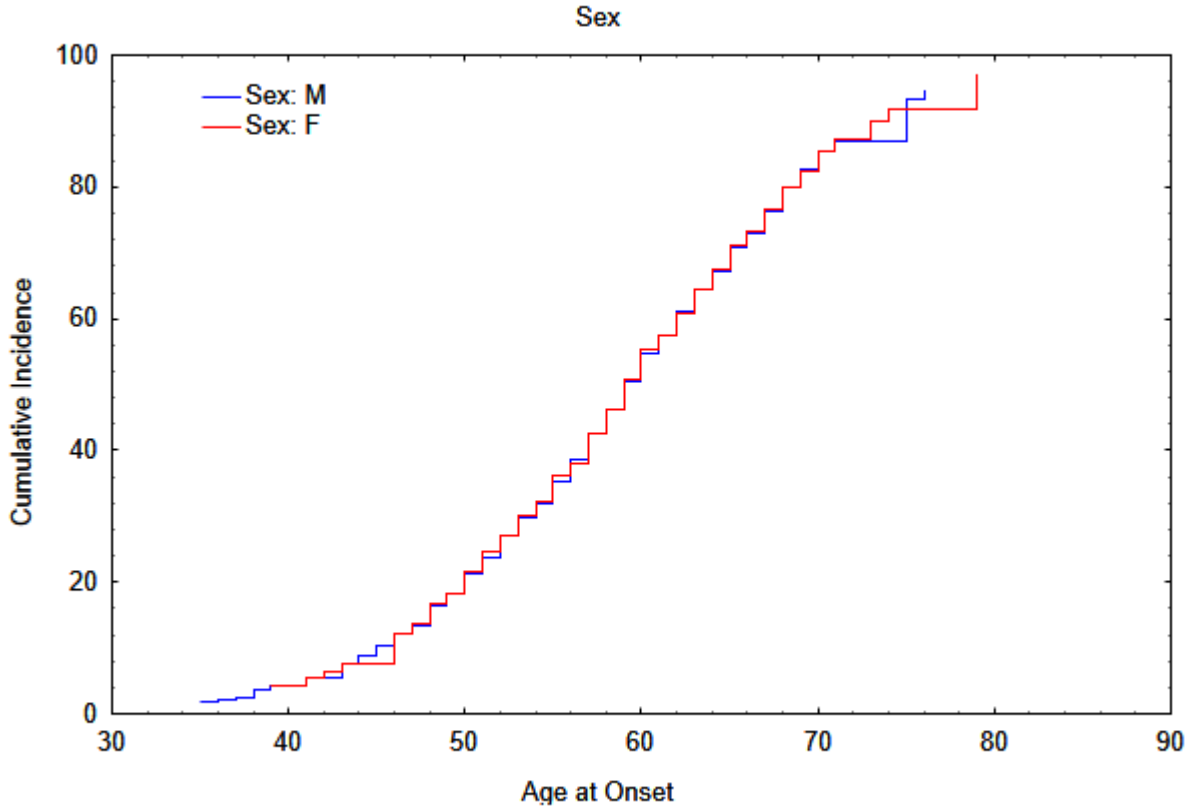
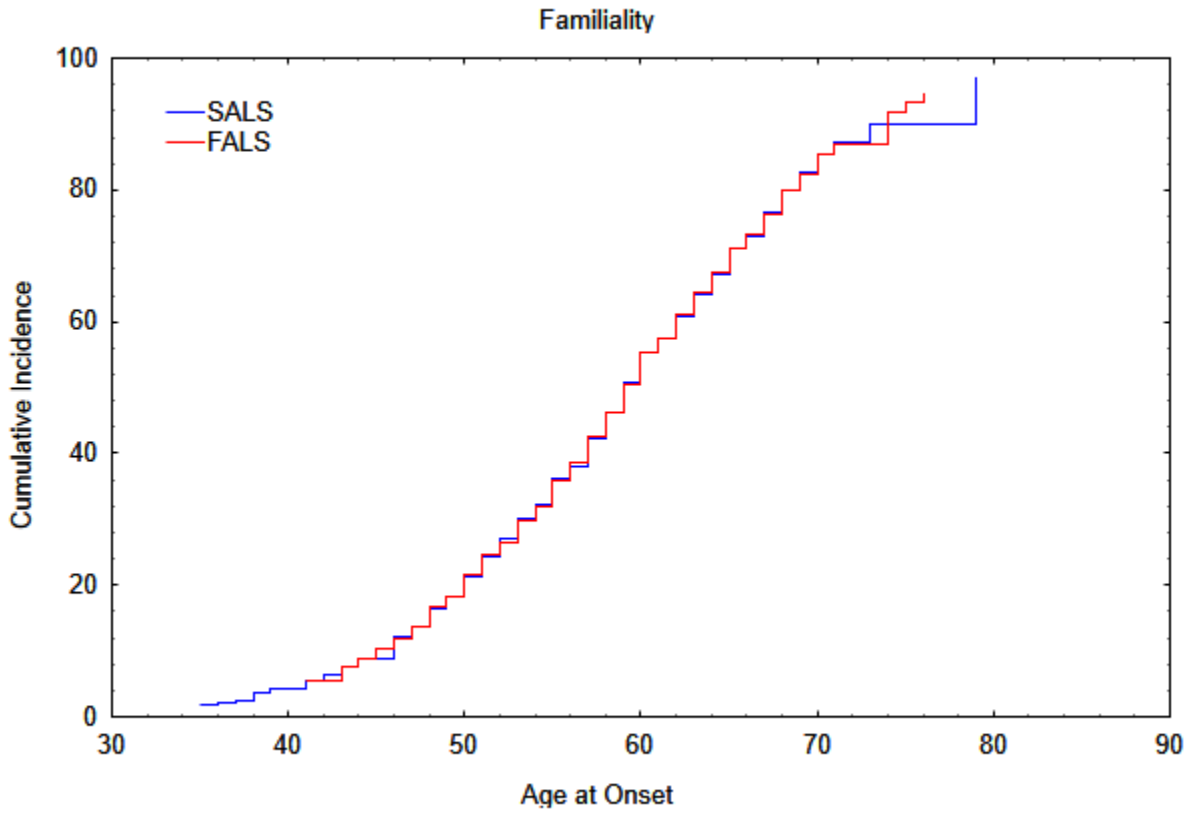
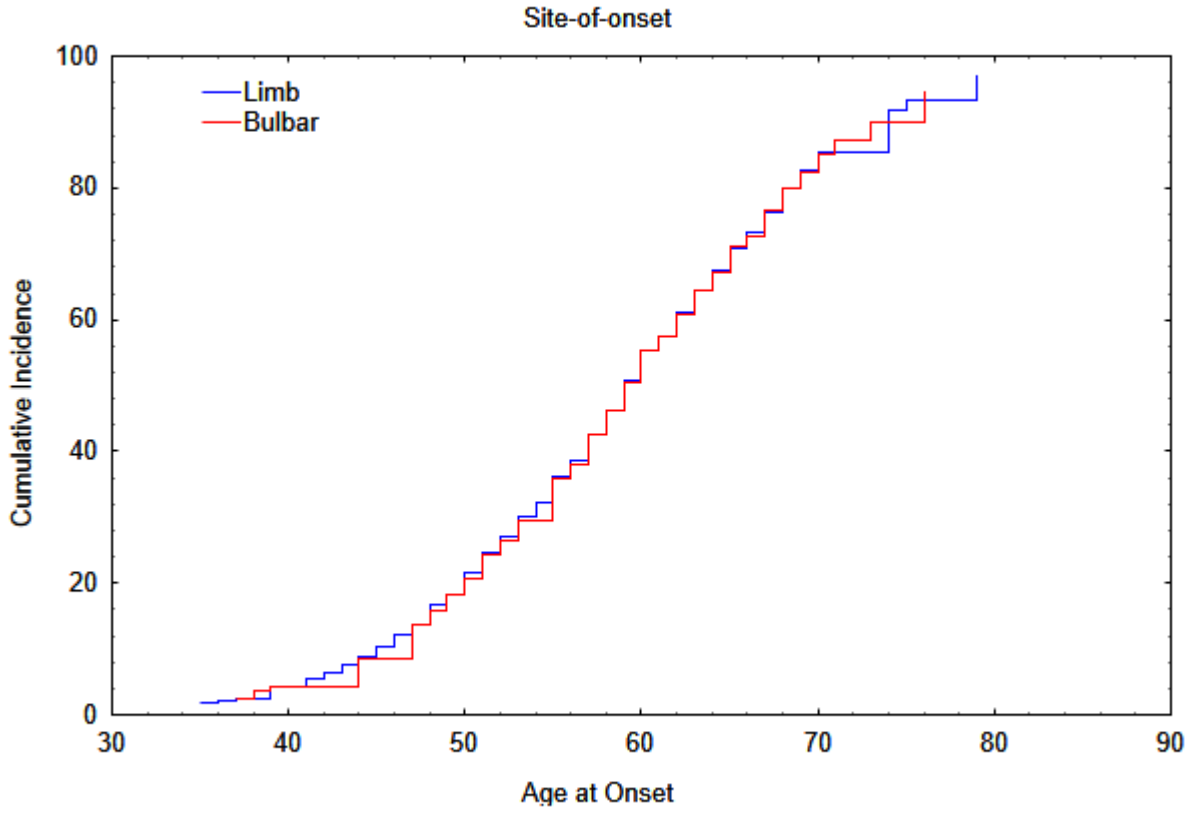



Familiality
SALS
FALS
Cumulative Incidence
Age at Onset
0
20
40
60
80
100
30
40
50
60
70
80
90


Site-of-onset
Limb
Bulbar
Cumulative Incidence
Age at Onset
0
20
40
60
80
100
30
40
50
60
70
80
90