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Supplementary Table 1. Cohort characteristics

	ALS	Control
Discovery cohort (Blauw et al., 2012)[1]	**2,290**	**2,775**
Country		
Netherlands	924	1729
Belgium	360	414
Germany	1006	632
Sex, male (%)	1,339 (58.5)	1,474 (53,1)
C9orf72 status available (%)	712 (31.1)	NA
Replication cohort: PCR	**753**	**603**
Country		
Netherlands	753	603
Sex, male (%)	433 (57.5)	347 (57.5)
C9orf72 status available (%)	753 (100)	NA
Clinical data available (%)[2]	748 (99.3)	NA
Replication cohort: Sanger sequencing	**764**	**767**
Country		
Netherlands	764	767
Sex, male (%)	478 (62.6)	469 (61.1)
C9orf72 status available (%)	759 (99.3)	NA
Clinical data available (%)[2]	688 (90.1)	NA
Replication cohort: ExpansionHunter	**2,438**	**906**
Country		
Belgium	338	176
Ireland	268	136
Netherlands	63	152
Spain	221	101
United Kingdom	1,112	274
United States of America	436	67
Sex, male (%)	1511 (62.0)	451 (49,8)
C9orf72 status available (%)	2,395 (98.2)	NA
Clinical data available (%)[2]	518 (21.1)	NA
Total replication cohorts: PCR + Sanger + Expansion Hunter	**3,955**	**2,276**
Total discovery + replication	**6,245**	**5,051**

[1] Data previously published in Blauw et al. (2012); duplicate samples were removed.
[2] Clinical data provided in Supplementary table 2.

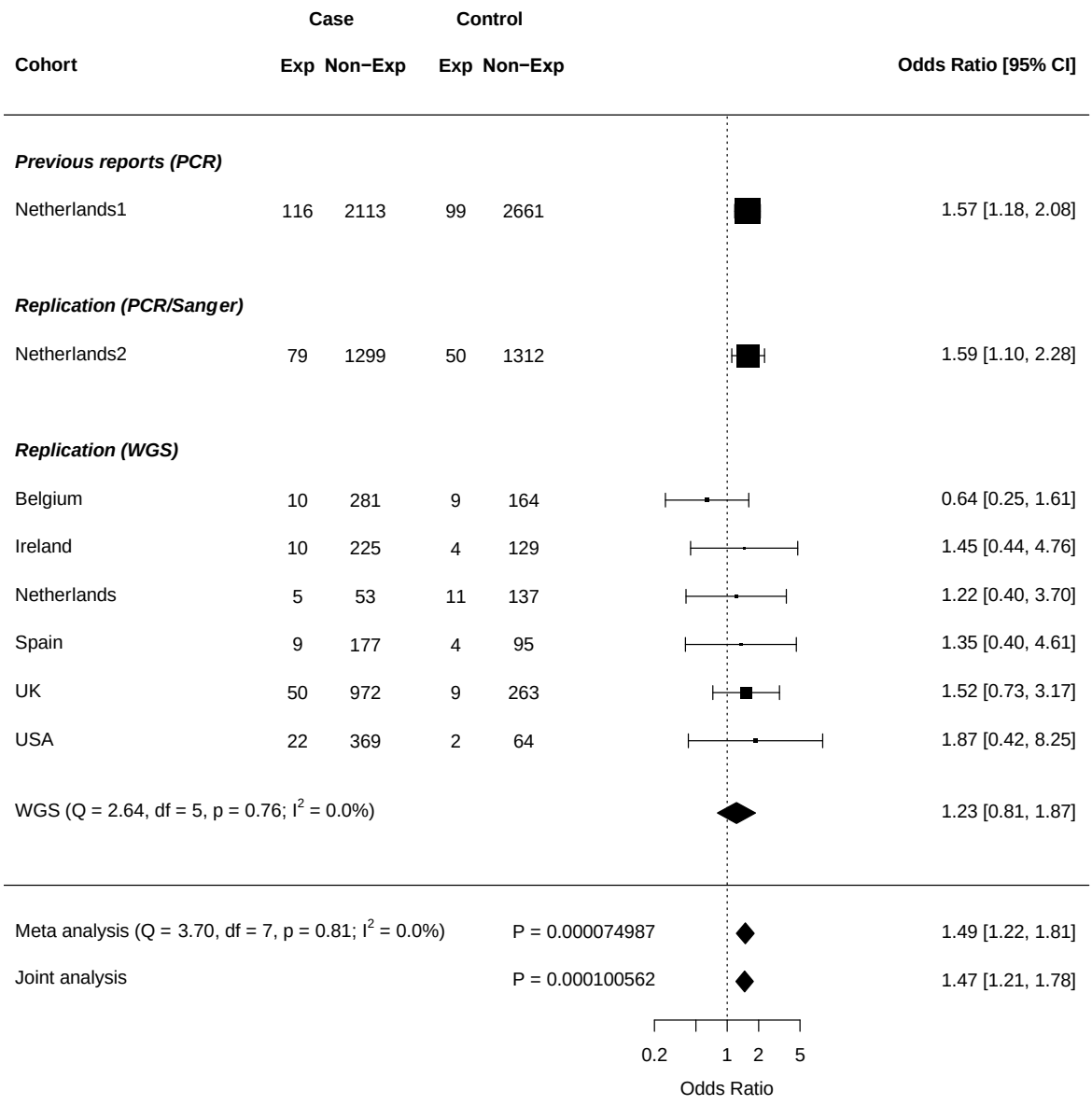
Supplementary Table 2. Clinical characteristics replication cohort

ALS patients with clinical data	**1,954**
Testing method	
PCR (%)	748 (38.3)
Sanger (%)	688 (35.2)
Expansion Hunter (%)	518 (26.5)
Country	
Ireland (%)	107 (5.5)
Netherlands (%)	1,499 (76.7)
United Kingdom (%)	348 (17.8)
Sex, male (%)	1,173 (60.0)
Mean age at onset, years (SD)	62.9 ± 10.9
Site of onset, bulbar (%)	669 (34.2)
C9orf72 expansion (%)	145 (7.4)
Median survival after onset, months (IQR)	32.0 [21.0-50.7]

Supplementary Table 3. Co-occurrence of *NIPA1* and C9orf72 repeat expansions

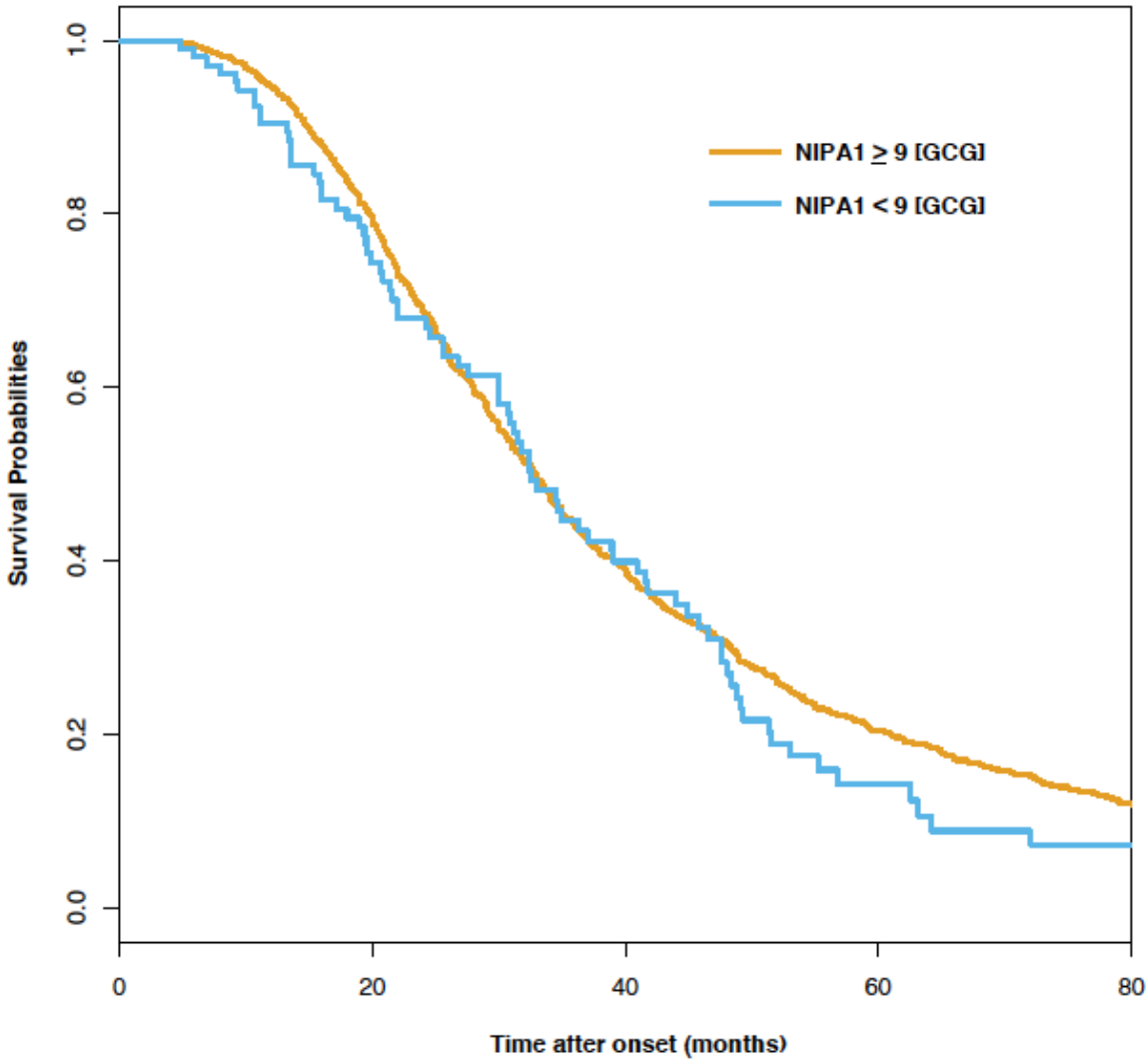
Genotype	ALS patients (n = 4619, %)	*C9orf72* carriers (n = 322, %)	Expected frequency (%)	Binominal *P*
NIPA1 + *C9orf72*	17 (0.37)	17 (5.27)	12.0 (0.26)	0.06

Co-occurrence of *NIPA1* exonic trinucleotide ([GCG] > 8) and *C9orf72* intronic hexanucleotide ([GGGGCC] ≥ 30) repeat expansion in 4619 ALS patients with known genotypes for both genes. Expected frequency was calculated from the total number of *C9orf72* expansion carriers (322) using the known frequency of *NIPA1* expansion in controls (189/5051, 3.74%).

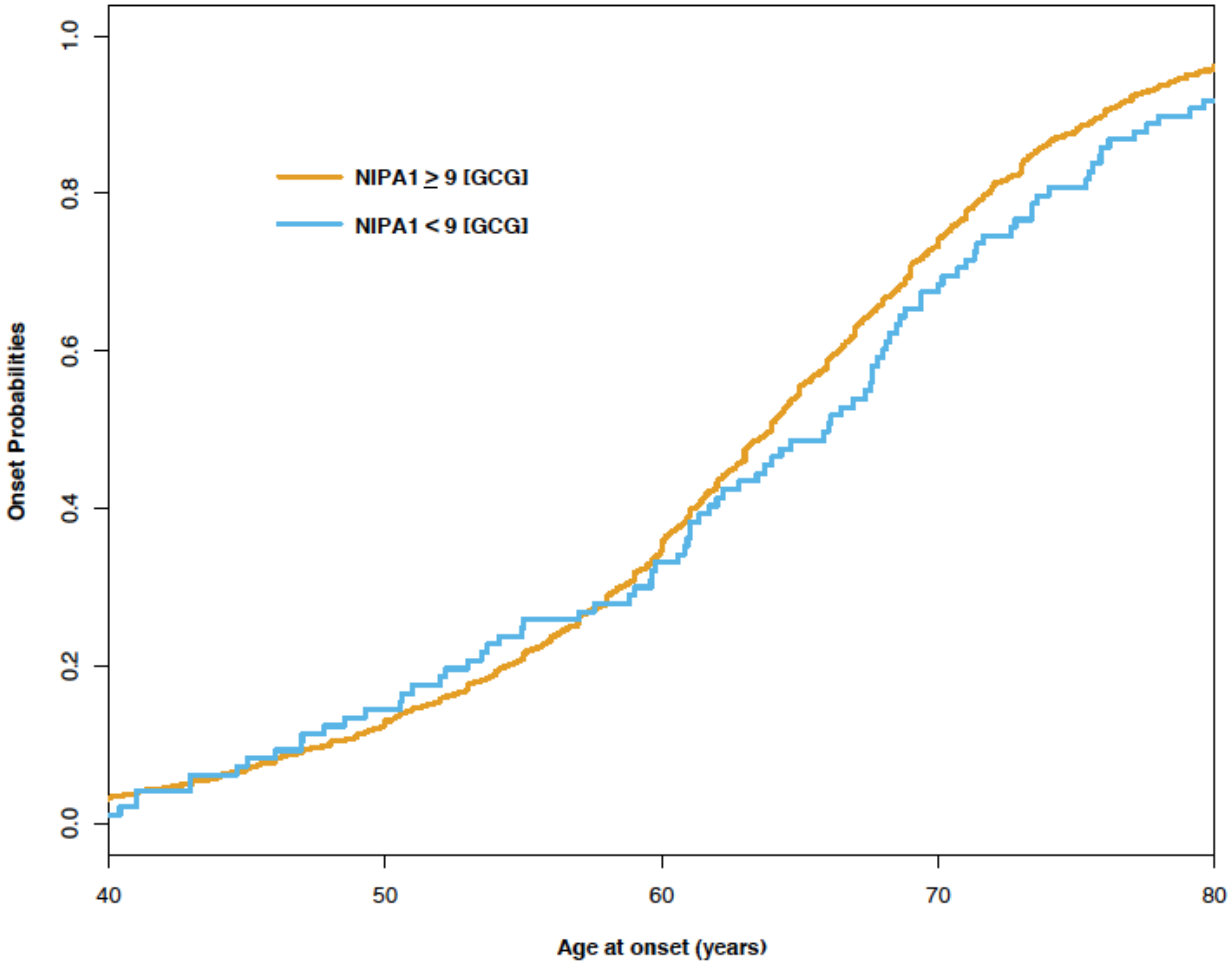


Supplementary Figure 1. *NIPA1* polyalanine repeat expansion meta-analysis excluding known mutant ALS gene carriers.

Forest plot for the fixed-effect meta-analysis and joint analysis on individual level data of the effect of expanded *NIPA1* polyalanine (>8 GCG repeats) on ALS risk without carriers of the pathogenic repeat expansion in *C9orf72* or nonsynonymous/loss-of-function variants in *SOD1*, *FUS* or *TARDBP.*



Supplementary Figure 2. Effect of *NIPA1* polyalanine repeat expansion on survival.
Kaplan-Meier plot showing the effect of *NIPA1* polyalanine repeat expansion on survival after onset of ALS. Cox-regression was corrected for sex, age at onset, site of onset and the presence of a *C9orf72* repeat expansion in the entire cohort of 1954 Dutch ALS patients.



Supplementary Figure 3. Effect of *NIPA1* repeat expansion on age at onset of ALS.
Plot of the effect of *NIPA1* GCG repeat expansion on age at onset corrected for sex, site of onset and the presence of a *C9orf72* repeat expansion in the replication cohort of 1954 ALS patients.