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Epidemiology and Survival Trends of Motor Neurone Disease in Northern Ireland from 2015-2019

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Data sharing and data accessibility
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abstract:
Objective:
This study evaluates the incidence, prevalence and survival trends of Motor Neurone Disease (MND) in Northern Ireland from 2015-2019.
Methods:
A capture-recapture analysis was performed using 5 independent data sources. Incidence and prevalence rates were standardised to the European standard population. Survival outcomes were analysed using Kaplan-Meier curves and Cox regression analysis.
Results:
Among 254 total cases of MND, capture-recapture analysis estimated 3 missing cases (case ascertainment 98.8%). Age standardised incidence of captured cases was 3.12 per 100000 (2.73,3.50) and standardised prevalence ranged from 9.45-6.49 per 100000 from 2015-2019. Standardised incidence and prevalence rates in 2006 were 1.4 and 3.3 per 100000 respectively.
Of identified cases: 133 (52.4%) were male; 94.5% had ALS; median age of onset was 67 yr; median time to diagnosis was 12 months (95% CI 11.2,12.8); survival from diagnosis was 12 months (95% CI 10.6,15.4); 25 (9.8%) reported a family history of MND or frontotemporal dementia; and a known MND-associated genetic mutation was identified in 7.9% of total cases, of which the most common was C9orf72 (5.7% of all patients). Factors associated with improved survival were younger age at onset, longer time to diagnosis, attendance at regional MND clinic, and initial neurology presentation as outpatient (all $P<0.001$).
Conclusion:
Incidence and prevalence of MND in NI has increased over the last 10 years, in line with increasing rates reported from other European countries. Improved survival was associated with younger age at onset, longer time to diagnosis, attendance at regional MND clinic and outpatient presentation to Neurology.

Introduction

Motor Neurone Disease (MND) is the term for a group of neurodegenerative diseases characterised by progressive motor neuron dysfunction. The most common form, Amyotrophic Lateral Sclerosis (ALS), often simply called MND, has an average survival from symptom onset of 2-4 years.[1] There are rarer, more slowly progressive forms with predominantly upper or lower motor neuron involvement, termed Primary Lateral Sclerosis (PLS) and Progressive Muscular Atrophy (PMA), respectively.[23] Epidemiological studies are important for identifying disease burden, guiding healthcare policy, and service planning.[45] Despite the relatively low incidence of MND it has a large socioeconomic impact and it is therefore important to monitor.[6] The number of MND cases is projected to increase by 69% over the next 20 years[4] and indeed multiple recent population studies have demonstrated an increasing incidence of MND.[578] Northern Ireland is well suited to the analysis of epidemiological trends in MND given its comprehensive countrywide prospective MND register beginning from 2004.[9] This study evaluates the incidence and prevalence trends in MND in Northern Ireland 2015-2019 compared to 2004-2006. We also evaluate factors associated with improved survival in MND.

Methods

Inclusion criteria. Cases were included of patients (1) aged ≥18 yr diagnosed with suspected, possible, probable or definite ALS according to revised El-Escorial criteria or PMA, Progressive Bulbar Palsy (PBP), or PLS, (2) where the diagnosis was made by a consultant neurologist (3) from 1st January 2015 until 31st December 2019, and (4) the patient was resident in Northern Ireland. Active cases diagnosed pre-2015 were recorded for prevalence evaluation.

Ethical approval. The NI MND register has ethical approval from the Health and Social Care Research Ethics Committee B (REC reference 20/NI/0122, previous reference 14/NI/0045). The BHSCT audit department approved the other data sources for use.

Data sources. The cases were ascertained from 5 different data sources: the NI MND register, Riluzole prescriptions from the single hospital pharmacy from which all prescriptions are processed, regional Neurophysiology records from the 2 clinical neurophysiology laboratories in NI, the Belfast Health and Social Care Trust (BHSCT) inpatient records, which houses the only Neuroscience Centre in NI and regional MND clinic records. The NI MND register is a prospective register aiming to capture all cases of MND in NI and is maintained by the regional MND care team. All regional neurophysiology records were individually reviewed for patients who had undergone electromyography by GMcC. The BHSCT audit department was the source of all other data. The Venn diagram representing ascertainment by each source was produced using DeepVenn.[10]

Data extraction. Data were extracted for demographic information, diagnostic evaluation, common clinical interventions for MND and survival outcomes. Cases were classified as familial if they had a first or second degree relative with MND or first degree relative with Frontotemporal dementia. Reference population data were taken from the annual mid-year population estimates of the NI Statistics and Research Agency. Prevalence calculations were determined from total number of active cases on 30th June each year when the mid-year population estimates are calculated. The crude incidence and prevalence figures were age and sex matched to the revised European Standard population (ESP) 2013.[11] Previous data from 2004-2006 were also standardised to the 2013 ESP for greater comparability.

Data analysis. Data analysis was performed using SPSS version 26, Microsoft Excel 2013 and R version 4.0.4. Continuous data were tested for normality using the Shapiro-Wilk test and non-normally distributed data were analysed using non-parametric tests. Capture-recapture analysis was performed using the sample coverage approach and analysed using the CARE1 program on R. This was used to evaluate case ascertainment but not for the incidence

figures as it would not facilitate age and sex standardization. Kaplan-Meier survival curves and Cox regression were used for univariate and multivariate survival analysis, respectively.

Results

Capture-Recapture Analysis. Over the 5 year study period we captured 254 incident cases of MND, with a Male:Female ratio of 1.1:1. The number of cases identified per year was78 (2015), 47 (2016), 59 (2017), 44 (2018) and 26 (2019). The patient characteristics are shown in Table 1. The NI MND register and Riluzole prescription lists had similar case ascertainment at 89.8% and 89.4%, respectively. The other sources had a lower ascertainment: neurophysiology records 58.3%, inpatient records 46.9%, MND clinic 39.4%. The overlap of the data sources are shown as a Venn diagram in Figure 1. The sample coverage capture-recapture analysis estimated 257 cases (95% CI 255,263) and the overall case ascertainment is therefore estimated at 98.8%.

MND Incidence in NI. The overall crude incidence rate was 2.71 per 100000 (95% CI 2.38,3.05). The age standardised incidence rate was 3.12 per 100000 (2.73,3.50). There was a higher incidence in males compared to females with standardised incidence rates of 3.48 (2.89,4.07) and 2.82 (2.32,3.32) per 100000 respectively. The overall standardised prevalence rate ranged from 9.45 per 100000 in 2015 to 6.49 per 100000 in 2019. The highest incidence in males was 18.7 per 100000 of those aged 80-85 and in females was 12.1 per 100000 in those aged 70-75. The variation by age is seen in Figure 2 and is compared to the rates from 2004-2006. The incidence of MND cases in 2004-2006 was 2.61 per 100000 (95% CI 1.99,3.24) when standardised to the 2013 ESP.

Familial and sporadic cases. 25 cases reported a family history of MND or frontotemporal dementia (FTD) (9.8%) and 51 patients overall (20.1%) had genetic testing for *C9orf72* gene and/or a familial ALS/FTD 42 gene panel, performed at Sheffield Diagnostic Genetics Services, England. The genes tested in this panel are shown in Supplementary Table 1. Cases with reported family history were much more likely to have genetic testing (76%) compared to 14% of those without a family history ($p < 0.001$). Of those who had genetic testing, there was a greater burden of known MND associated gene mutations identified in familial cases (14/19) compared to sporadic (6/32). Again this difference was statistically significant ($p < 0.001$). The most commonly identified pathogenic variant was a *C9orf72* hexanucleotide repeat expansion. The other gene mutations identified are shown in Table 1 and the proportions identified in familial and sporadic cases are shown in Figure 3.

Most patients (59.4%) had spinal onset MND, with 40.2% having bulbar onset. There was one patient with respiratory muscle onset.

Clinical Interventions. There was documented evidence of 90.6% of all patients having been issued with Riluzole therapy (90.6%). 108 patients (42.5%) had a gastrostomy, with 87% of those being a radiologically inserted gastrostomy (RIG) and 13% a Percutaneous Endoscopic Gastrostomy (PEG). Gastrostomy tubes were inserted at a median of 4 months from diagnosis (95% CI 2.7,5.4). Patients with bulbar onset MND were more likely to have a gastrostomy than those with spinal onset (57.8% and 32.4% respectively, $P < 0.001$). The 30 day mortality following gastrostomy was 3.2% for RIG, 7.1% for PEG and 3.7% overall. The median survival following gastrostomy was 292 days (95% CI 248.5,335.5).

Over one-third (36.6%) of patients were established on Non-Invasive Ventilation (NIV), which was Bilevel Positive Airway Pressure (BiPAP) in all but 1 patient who received Continuous Positive Airway Pressure (CPAP). 2 patients had a tracheostomy, inserted for stridor in both cases.

Time to diagnosis. The median time to diagnosis from first symptom onset was 12 months (95% CI 11.2, 12.8) and median survival after diagnosis was 12 months (10.6, 15.4). Many patients were initially reviewed in another medical department before Neurology (30.7%) including ENT, Orthopaedics, Neurosurgery and Care of the Elderly. Those seen by another

specialist team first had a median time to diagnosis of 12 months (10.6, 13.4), compared to 11 months (9.9, 12.1) where neurology was first referral, a difference that was not statistically significant (p= 0.082).

Survival analysis. There was a large variation in survival times based on type of MND, with PLS having the longest median survival time of 81 months from symptom onset (95%CI 62.5, 99.5), followed by UMN predominant ALS (61 months; 15.6, 106.4), PMA (53 months; 17.1, 88.9), LMN predominant ALS (34 months; 25.8, 42.2) and classical ALS (25 months; 22.4,27.6). There was a significant difference in survival between groups as shown by the Kaplan Meier curve in Figure 4a (log rank p=0.002). The median overall survival from symptom onset was 28 months (25.6, 30.4).

Most patients had their first presentation to Neurology as an outpatient (74.4%) and this was associated with a longer survival from symptom onset of 31 months (95% CI 27.5,34.5) compared to inpatient presentation (16 months; 11.7,20.3), log rank p <0.001. Patients whose first Neurology point of contact was as an inpatient were also less likely to be followed up at the regional MND clinic (P <0.001). Patients who attended the regional MND clinic had a longer median survival time (30 months, 95% CI 26.5.33.5) than those who did not (20 months; 16.4,23.6), with log rank p=0.004. Patients with bulbar onset disease had a worse prognosis (log rank p=0.003). Median survival for bulbar site of onset was 23 months (19.7,26.3) compared to spinal onset at 33 months (28.0, 38.0). These data are shown in Figure 4b.

Factors affecting survival were analysed using a multivariate Cox regression analysis shown in Table 2. When adjusting for other variables, the factors showing a significant effect on survival were younger age at onset (HR 1.03 for each year increase in age), longer time to diagnosis (HR 0.93 for each month delay to diagnosis), first presentation to Neurology as an inpatient (HR 2.13) and attendance at the tertiary, multidisciplinary regional MND clinic (HR 0.57), with P <0.001 for all 4 factors. Type of MND was also a factor, with PLS having a significant survival benefit over ALS (HR 0.34, P= 0.04)

Discussion

The incidence and prevalence rates in NI are higher than previously reported in 2006[9]Part of this variation may be explained by the change in reference population as the EFP was revised in 2013 to reflect a more aging population and, for diseases that are more common in the elderly, would result in higher estimates than the 1976 version.[11] However, standardising the 2004-2006 data to the 2013 ESP still gives a lower standardised incidence of 2.61 per 100000 compared to this study at 3.12 per 100000 showing that this does not completely account for the increased rates. Figure 2 shows that the increase in cases is largely due to more patients with MND diagnosed aged ≥65 yr and likely reflects the aging population. However, the multiple data sources used in this study may also have given greater case ascertainment than the 2004-2006 study and be partially responsible for the increased rates.

The rising figures are in keeping with data reported from many other prospective European MND registers. In the Republic of Ireland, incidence rates have slightly increased from 2.1 per 100000 in 1997 to 2.5 in 2010, with prevalence 6.8 per 100000 in 2010 [1213]. Reported incidence in recent European studies from Scotland, England, Norway, Italy, Germany and Sweden have ranged from 1.6-3.8 per 100000.[57,141516,17] A 2017 meta-analysis of 44 studies over 45 geographical areas calculated a standardised incidence of 1.68 per 100000, although this included studies from 1970s and from Asia where there have been several studies reporting lower incidence.[18]

A capture-recapture analysis was undertaken to assess completeness of case ascertainment, as has been suggested for epidemiological studies and used in many ALS/MND studies.[919,20] There are multiple methods for creating a capture-recapture estimate. Most, for example Petersen and Chapman models, require 2 case sources and if more than 2 sources are present

predictive modelling is used to identify the best combination of 2 sources to fit the data.[21] Chao's sample coverage approach used here allows for analysis of multiple sources, does not require the same degree of source independence and has been shown to give more reliable results.[20,22] The analysis estimated only 3 missing cases, showing a high case ascertainment in the study. However, there is likely a degree of interdependence between the sources, e.g. patients attending MND clinic are more likely to be put on the MND register, and this often leads to an underestimation of missed cases.[21]

Some 9.8% of cases were familial, in keeping with commonly reported figures of around 10%.[323] Notably, mutations in genes associated with MND were identified in 18.8% (6/32) of the sporadic cases who were tested. Overall, a *C9orf72* mutation was the most commonly found pathogenic variant (14 cases), there were 2 SOD1 mutations and also 4 mutations in genes that while not definitively pathogenic, are disease modifiers in MND (ATXN2, FIG4 and TBK1). A recent UK study identified pathogenic mutations in 21% of patients, 93% of whom had no family history, with *C9orf72* expansion as the most common cause.[24] This highlights the importance of considering genetic testing in sporadic as well as familial cases.

Most patients were treated with Riluzole (90.6%). This is in keeping with UK prescribing practice, with a recent study in Scotland showing Riluzole being offered to 86.5% of patients between 2015-2020.[25] The Riluzole prescription lists were also an excellent source for case ascertainment, identifying 89.4% of patients. Riluzole sales records have previously been shown to correlate well with MND prevalence[26] and could be a useful way of assessing case ascertainment of population based registers.

The median survival from symptom onset was 28 months. This is similar to the median survival of 2.39 years reported from the Republic of Ireland register from 1995-2010. [27] There was a large difference in survival times based on the type of MND, with PLS having the longest survival and classical ALS the shortest. This was significant in the Kaplan-Meier analysis and the multivariate Cox Regression, despite the low number of PLS cases. Younger age at onset, longer time to diagnosis and care in a specialized MND multidisciplinary clinic were also associated with improved survival and have been described as good prognostic features in other studies.[1,2] We also identified worse survival times for patients with an initial presentation to Neurology as an inpatient. This may be due to patients presenting with severe symptoms requiring hospitalization, e.g critical dysphagia or respiratory failure.

Some 42.5% of patients had a gastrostomy, with RIG the most common method for insertion, at 87%. RIG has the benefit of not requiring conscious sedation and has been shown to have lower 30 day mortality than PEG.[28] As expected, gastrostomy was more commonly inserted in patients with bulbar onset MND. The overall 30 day mortality from gastrostomy at 3.7% compares favourably to a meta-analysis showing 30 day mortality from RIG and PEG to be 6% and 10% respectively in patients with MND.[28] The median survival time following gastrostomy of 292 days (9.4 months) is also comparable to recent systematic reviews.[28,29]

Conclusion

The incidence and prevalence rates of MND in Northern Ireland have risen over the last 10-15 years in keeping with results reported from other European registries. Capture-recapture estimates are important for assessing case ascertainment of epidemiological studies to try to provide more accurate estimates. Factors associated with improved survival in this study were the type of MND, younger age of onset, longer duration before diagnosis, outpatient presentation to Neurology services and attendance at a regional MND multidisciplinary clinic.

Tables and Figures Legends

Clinical characteristics of Incident cases 2015-2019		
Gender (n (%))	Male	133 (52.4)
	Female	121 (47.6)
Age at onset (median (95% CI))	67 (65.3,68.7)	
Onset to diagnosis months (median (95% CI))	12 (11.2,12.8)	
Diagnosis to death months (median (95% CI))	12 (9.8, 14.2)	
Onset to death months (median (95% CI))	28 (25.6, 30.4)	
Site of onset (n (%))	Bulbar	102 (40.2)
	Spinal	151 (59.4)
	Respiratory	1 (0.4)
Type of MND (n (%))	ALS	208 (81.9)
	UMN Predominant ALS	12 (4.7)
	LMN Predominant ALS	20 (7.9)
	PMA	7 (2.8)
	PLS	7 (2.8)
El Escorial criteria for ALS cases (n (%))	Suspected	1 (0.4)
	Possible	41 (17.1)
	Probable	132 (55.0)
	Definite	63 (26.3)
	Unknown	3 (1.3)
Family history (n (%))	Yes	25 (9.8)
	No	229 (90.2)
Genetic testing for MND genes (n (%))	Yes	51 (20.1)
	No	203 (79.9)
MND gene mutation (n (%))	Yes	20 (7.9)
	No	234 (92.1)
Types of mutation (n (%))	C9orf72	14 (5.7)
	SOD1	2 (0.8)
	ATXN2	2 (0.8)
	FIG4	1 (0.4)
	TBK1	1 (0.4)

Table 1- Clinical characteristics of included patients

Table 2 Multivariate Cox Regression analysis on factors associated with effect on survival in MND

		number	Hazard Ratio	95% CI	P value
gender	female	121	1	Reference	
	Male	130	1.21	0.91,1.61	0.189
Age at onset			1.03	1.02,1.05	**<0.001**
Length from symptom onset to diagnosis (months)			0.93	0.91,0.95	**<0.001**
First presentation to neurology	outpatient	189	1	Reference	
	inpatient	62	2.13	1.5,3.0	**<0.001**
type of MND	overall				0.219
	ALS	205	1	Reference	
	UMN predominant	12	0.91	0.44,1.9	0.802
	LMN predominant	20	0.88	0.5,1.53	0.640
	PLS	7	0.34	0.12,0.95	**0.04**
	PMA	7	0.59	0.25,1.35	0.209
site of onset	overall				0.394
	bulbar	101	1	Reference	
	spinal	149	0.86	0.62,1.2	0.363
	resp	1	0.316	0.04,2.4	0.266
MND clinic	no	106	1	Reference	
	yes	145	0.57	0.42,.78	**<0.001**
Riluzole	no	23	1	Reference	
	yes	228	1.15	0.69,1.93	0.593
Gastrostomy	no	143	1	Reference	
	yes	108	0.82	0.59,1.14	0.244
NIV	no	158	1	Reference	
	yes	93	1.04	0.77,1.41	0.802

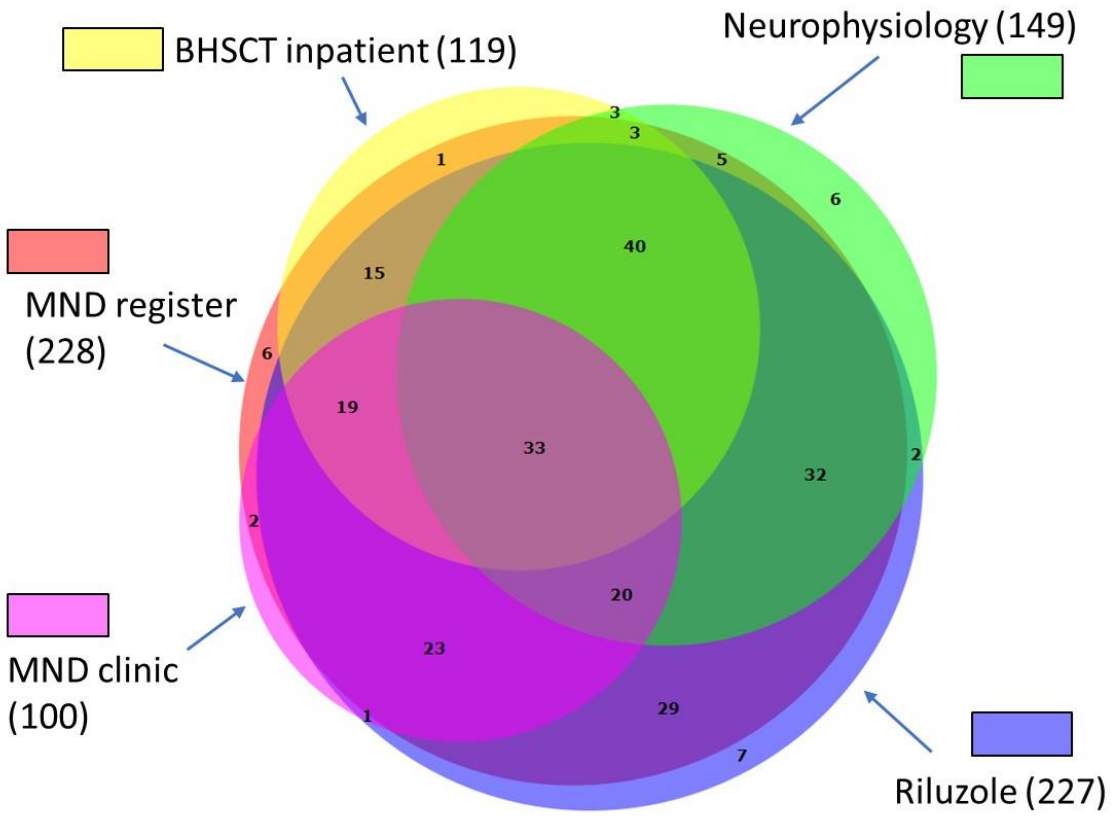

Figure 1- Proportional Venn diagram showing case ascertainment from each data source with total case numbers identified from each source in brackets

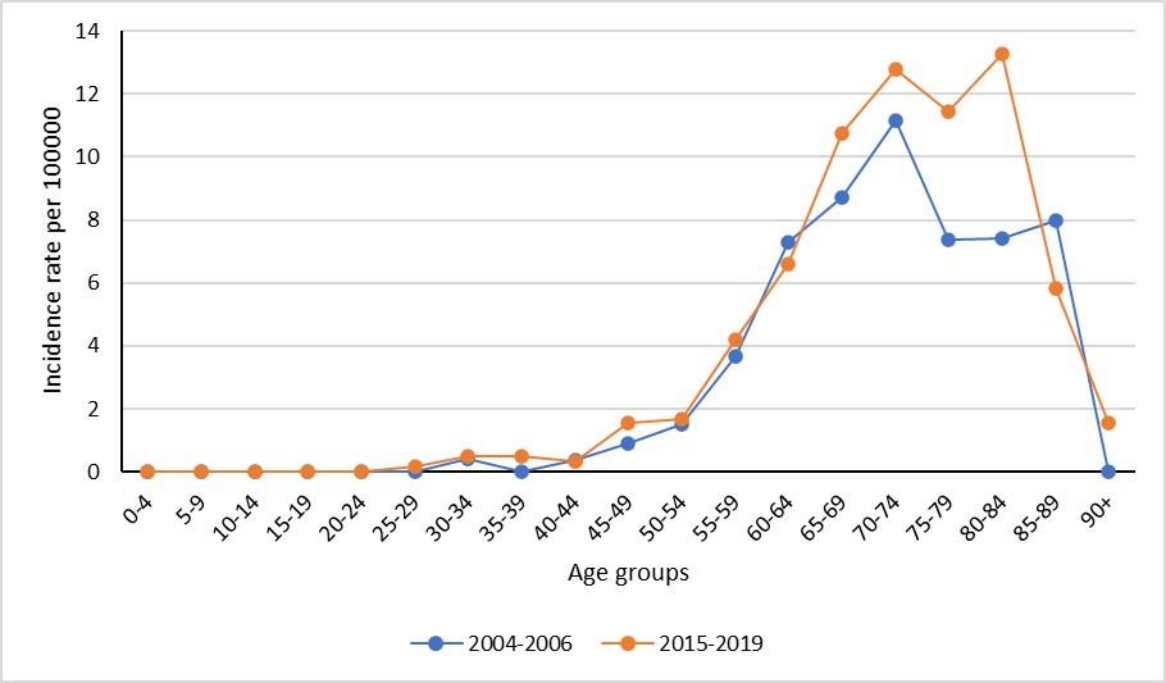

Figure 2- Comparison of MND incidence between 2004-2006 and 2015-2019

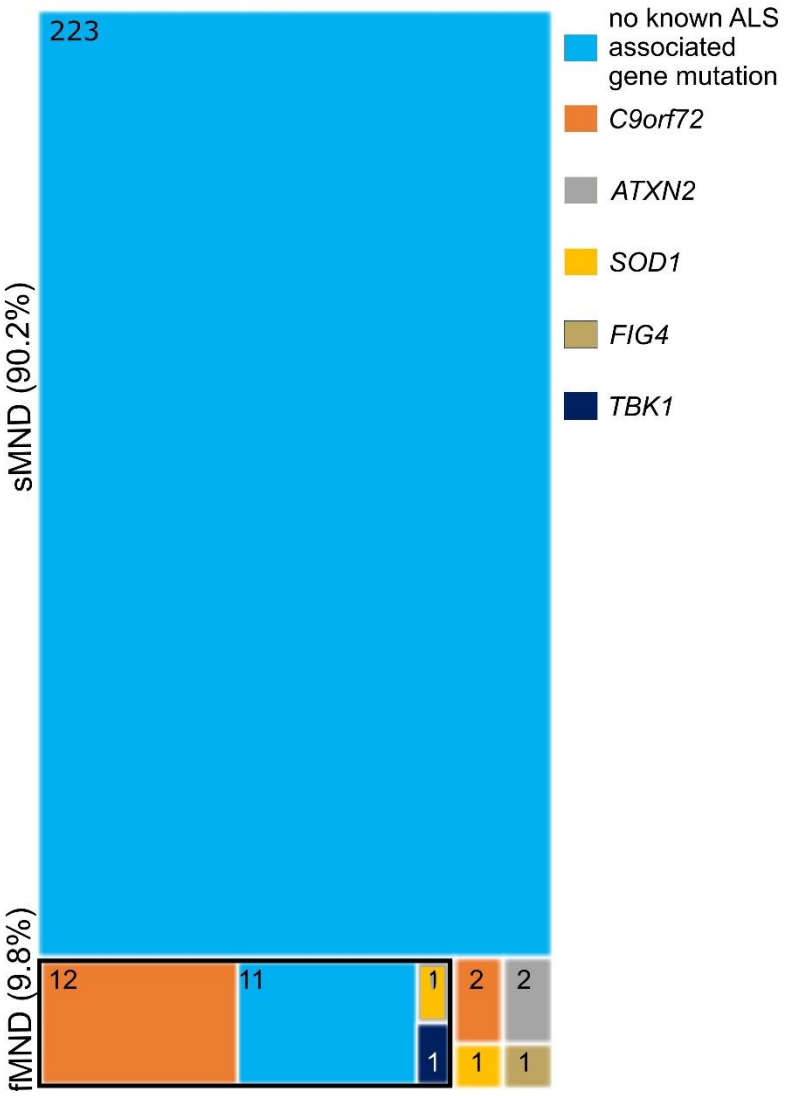

Figure 3- Treemap showing the distribution of genetic basis among the Northern Irish MND population. The full rectangle represents 100% of all MND cases. The familial MND (fMND) are highlighted in black (9.8% of all MND cases). The two light blue blocks represent those with no known ALS-associated gene mutation among sporadic and familial cases. Cases with known mutations are represented in the other blocks, broken down by affected gene. The color code for each gene is preserved between familial and sporadic cases. The size of each block is proportional to the percentage of MND. The number of patients in each category is indicated in each square.

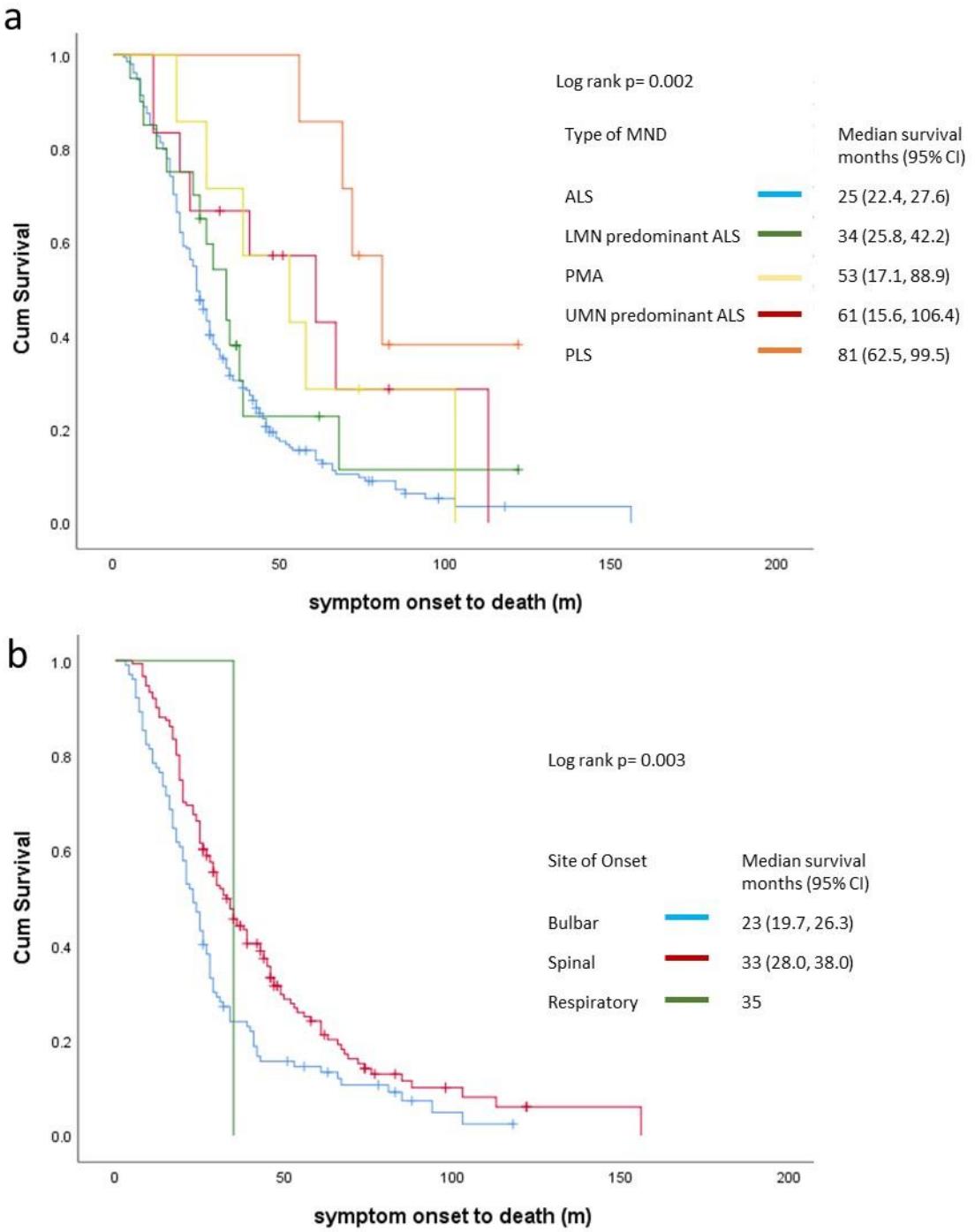

Figure 4 - Kaplan Meier curves showing survival of patients investigating for effect of 4a Type of MND and 4b site of first muscular weakness.

Condition	OMIM ID	Gene
Primary lateral sclerosis, juvenile, PLSJ	606353	ALS2
Amyotrophic lateral sclerosis 9, ALS9	611895	ANG
Familial Amyotrophic Lateral Sclerosis		ANXA11

Familial Amyotrophic Lateral Sclerosis		ARHGEF28
Spinocerebellar ataxia 2, SCA2	183090	ATXN2
Frontotemporal dementia and/or amyotrophic lateral sclerosis 2, FTDALS2	615911	CHCHD10
Amyotrophic lateral sclerosis 17, ALS17	614696	CHMP2B
Cerebrotendinous xanthomatosis, CTX	213700	CYP27A1
Familial Amyotrophic Lateral Sclerosis		DAO
Neuropathy, distal hereditary motor, type VIIB, HMN7B	607641	DCTN1
Amyotrophic lateral sclerosis 19, ALS19	615515	ERBB4
Familial Amyotrophic Lateral Sclerosis		EWSR1
Amyotrophic lateral sclerosis 11, ALS11	612577	FIG4
Amyotrophic lateral sclerosis 6, with or without frontotemporal dementia, ALS6	608030	FUS
Spastic paraplegia 46, autosomal recessive, SPG46	614409	GBA2
Frontotemporal lobar degeneration with TDP43 inclusions, GRN related	607485	GRN
Amyotrophic lateral sclerosis 20, ALS20	615426	HNRNPA1
Inclusion body myopathy with early-onset Paget disease with or without frontotemporal dementia 2, IBMPFD2	615422	HNRNPA2B1
Frontotemporal Dementia, FTD	600274	MAPT
Amyotrophic lateral sclerosis 21, ALS21	606070	MATR3
Amyotrophic lateral sclerosis, susceptibility to, ALS1	105400	NEFH
Familial Amyotrophic Lateral Sclerosis		NEK1
Amyotrophic lateral sclerosis 12, ALS12	613435	OPTN
Amyotrophic lateral sclerosis 18, ALS18	614808	PFN1
Amyotrophic lateral sclerosis, susceptibility to, ALS1	105400	PRPH
Amyotrophic lateral sclerosis 4, juvenile, ALS4	602433	SETX
Amyotrophic lateral sclerosis 16, juvenile, ALS16	614373	SIGMAR1
Amyotrophic lateral sclerosis 1, ALS1	105400	SOD1
Spastic paraplegia 4, autosomal dominant, SPG4	182601	SPAST
Amyotrophic lateral sclerosis 5, juvenile, ALS5	602099	SPG11
Spastic paraplegia 20, autosomal recessive, SPG20	275900	SPG20
Frontotemporal dementia and/or amyotrophic lateral sclerosis 3, FTDALS3	616437	SQSTM1
Familial Amyotrophic Lateral Sclerosis		SS18L1
Familial Amyotrophic Lateral Sclerosis		TAF15
Amyotrophic lateral sclerosis 10, with or without FTD, ALS10	612069	TARDBP
Frontotemporal dementia and/or amyotrophic lateral sclerosis 4, FTDALS4	616439	TBK1
Amyotrophic lateral sclerosis 22 with or without frontotemoral dementia, ALS22	616208	TUBA4A
Amyotrophic lateral sclerosis 15, with or without frontotemporal dementia, ALS15	300857	UBQLN2
Amyotrophic lateral sclerosis 8, ALS8	608627	VAPB
Amyotrophic lateral sclerosis 14, with or without frontotemporal dementia, ALS14	613954	VCP
Familial Amyotrophic Lateral Sclerosis		VPS54
Pontocerebellar hypoplasia type 1A, PCH1A	607596	VRK1

Supplementary Table 1- 42 gene panel for Amyotrophic Lateral Sclerosis/ Frontotemporal Dementia

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