

# Motor Neurone Disease (MND/ALS) among Maltese in Malta and Australia: many sporadic cases were related

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## Abstract

**Objective:** to look for genetic links between cases of MND.

**Method:** to search for ancestors of Maltese cases dying in Malta and Australia and to record dispensations for consanguineous marriages.

**Results:** the median age of death was similar in both countries and in Malta was similar for men and women. Almost 45 % of the cases were related to one or more other cases: however, more than half were sporadic and widely dispersed.

**Conclusions:** MND is not affected by emigration to the southern hemisphere and different life styles. Many MNDs are related and may represent a sub-group.

## Keywords

amyotrophic lateral sclerosis, Australia, consanguinity, kinship, Malta, motor neurone disease.

## Introduction

'The clinical and biological evidence that ALS [amyotrophic lateral sclerosis] or motor neurone disease, MND) cannot be a single disorder...allows for a novel approach to pharmacological strategies.'<sup>1</sup> This study suggests that many of the sporadic cases are related to other cases and may form a sub-species of the disorder.

The islands of Malta and the smaller Gozo lie between Sicily and Africa and have a compact population with good medical services and marriage records. Until WWII all were Roman Catholic, most lived in small villages and often married within local groups. The Maltese are a blend of Arab and South European peoples with some from the Knights Templar and more recent additions from eg Italy. With the British dockyard and administration, some British men married Maltese girls, mainly in Valletta, Senglea and Cospicua. When infant mortality fell dramatically in the late 1940's, Maltese children were encouraged to emigrate, especially to Australia where death certificates record the place of birth (eg Malta). Before 1990 few Maltese death certificates recorded motor neurone disease (MND/ALS).

## Materials and methods

This study comprises 196 Maltese whose death certificates included a diagnosis of MND and six whose diagnosis has been confirmed by their neurologists. Forty eight had emigrated to Australia, two had been born in the USA, but had returned to Malta, and one was resident in England. Twelve had been born in Gozo, two of whom died in Australia. One death in the USA and three in Britain were found from Maltese newspapers. The two earliest births were in 1898 and the latest was in 1979 (he died age 20 yr). The Health Information Unit (Malta) kindly gave me verified deaths from MND since 1990 and Dr Geoffrey Dean provided earlier cases from Malta and Australia. State registries in Australia sent photocopies of deaths from MND of those born in Malta. Data Protection Law as interpreted by Victoria State, Australia has meant that the last case was from November 2004. Initially, all were traced to their great-grand parents, but some rare surnames suggested that cases might be linked, so I followed their ancestors to about 1820 or so. Marriages and births were traced in the

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Public Registry and, before 1863, in parish records. Some marriages were never registered, others were made overseas (Egypt, Crete, Gibraltar, Libya, etc), a few were not blessed by the church, some children were adopted and others were born without naming the father. Some parish registers omit the mother's maiden name. One father was untraceable, one great grand-parent was 'unknown' and one case was adopted. One Italian and four British cases were excluded. Marriages were checked for dispensations for consanguinity in the Curias of Malta and Gozo and in parish records. Consanguinity is shown by roman numerals eg II is a marriage of two first cousins, and by double lines between bride and groom. All marriages to foreigners were followed, as many had ancestors who had married Maltese. Some marriages in Gibraltar, Tunis and USA were traced, but Egyptian records were destroyed in 1956.

**Results**

**Diagnosis**

All cases were diagnosed as 'MND'. Cases 34 and 132 were diagnosed as 'pseudo bulbar palsy', cases 38 and 111 as 'progressive MND' and 32 as 'mixed bulbar and pseudo bulbar palsy'.

**Age at death**

The median age at death was very similar for men and women in Malta, for those from Gozo and for the emigrants to Australia although the ranges were different (Table 1, Fig. 1). Most of the emigrant children to Australia were boys and the median domicile was 31 yr (Table 1). The age at death was probably typical (Fig. 1) although the two youngest were possibly rare.<sup>2</sup> Of those in Malta, 36 died in the three months December (13), January (12) and February (11) and only 52 in the other nine months

**Table 1:** Median age at death of MNDs

		N	Median age	Range yr	Median domicile
Gozo		16	64 yr	28 - 80	
Malta	Men	84	64 yr 5m	20 - 88	
	Women	57	63 yr 7m	34 - 84	
Australia	(34 men, 14 women)	48	64 yr	36 - 90	31 yr range 11-57

**Kinship**

There were 80 (45%) cases with links to at least one other. I have used kinship as a neutral term to describe these links. There are probably 22 (11 %) familial cases

in Kinship 2 (Fig. 2) and Kinship 1 (Fig. 4). Only Kinships 1, 2 and 17 had cases in two generations. There were groups with 16, 10, 9, 6 and 4 cases, five groups with three cases and 14 groups with two in each (see Figures).

**Location**

I have used the 1901 populations to compare the incidence in different parishes, based on the homes of the grand-parents. Some kinship groups were based on one parish, while some were from eight or more villages. A few older parishes were very large and have since been reduced. Where parish boundaries are adjacent, a marriage from two parishes might be between near neighbouring farms. The four areas with the greatest incidence included the three large kinship groups (Table 2).

**Table 2:** Incidence of grand-parents of MNDs by parishes

Parish or town	Population	No. of cases	No. of cases		Cases 0/00
	1901 census	sporadic	kinship	Total	
Area Y#	c 6,000	8	9.5	17.5	2.7
Village F+	c 6,000	1	10.5	11.5	2
Area H	c 6,000	3.5	9	12.5	1.95
Villages I and J#	c 8,000	7	7	14	1.75
Village D	c 8,000	8.5	3.5	12	1.45
Village E	c 7,000	2.5	7.5	10	1.4
Parish V*	c 2,000	1	2	3	1.25
Valletta, Floriana	22,680	19	9.5	28.5	1.25
Village C	c 3,000	3	0.5	3.5	1.1
Cospicua, Senglea	20,241	10	3	13	0.58
Hamrun	10,293	1.5	-	1.5	0.15

**Note:**

# These adjacent parishes were extensive with one large kinship group common to both (kinship 1, Fig. 3)

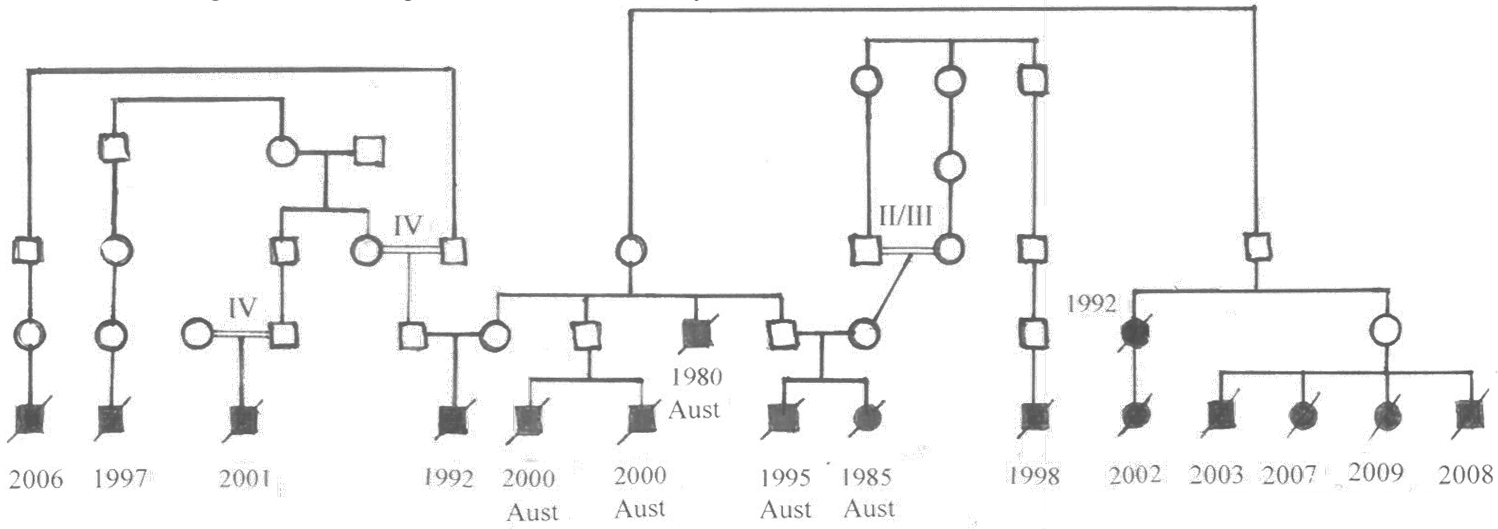
+ This was the centre of kinship 2 (Fig. 1).

\* This isolated parish shared links with Gozo (kinship 20, Fig. 2).

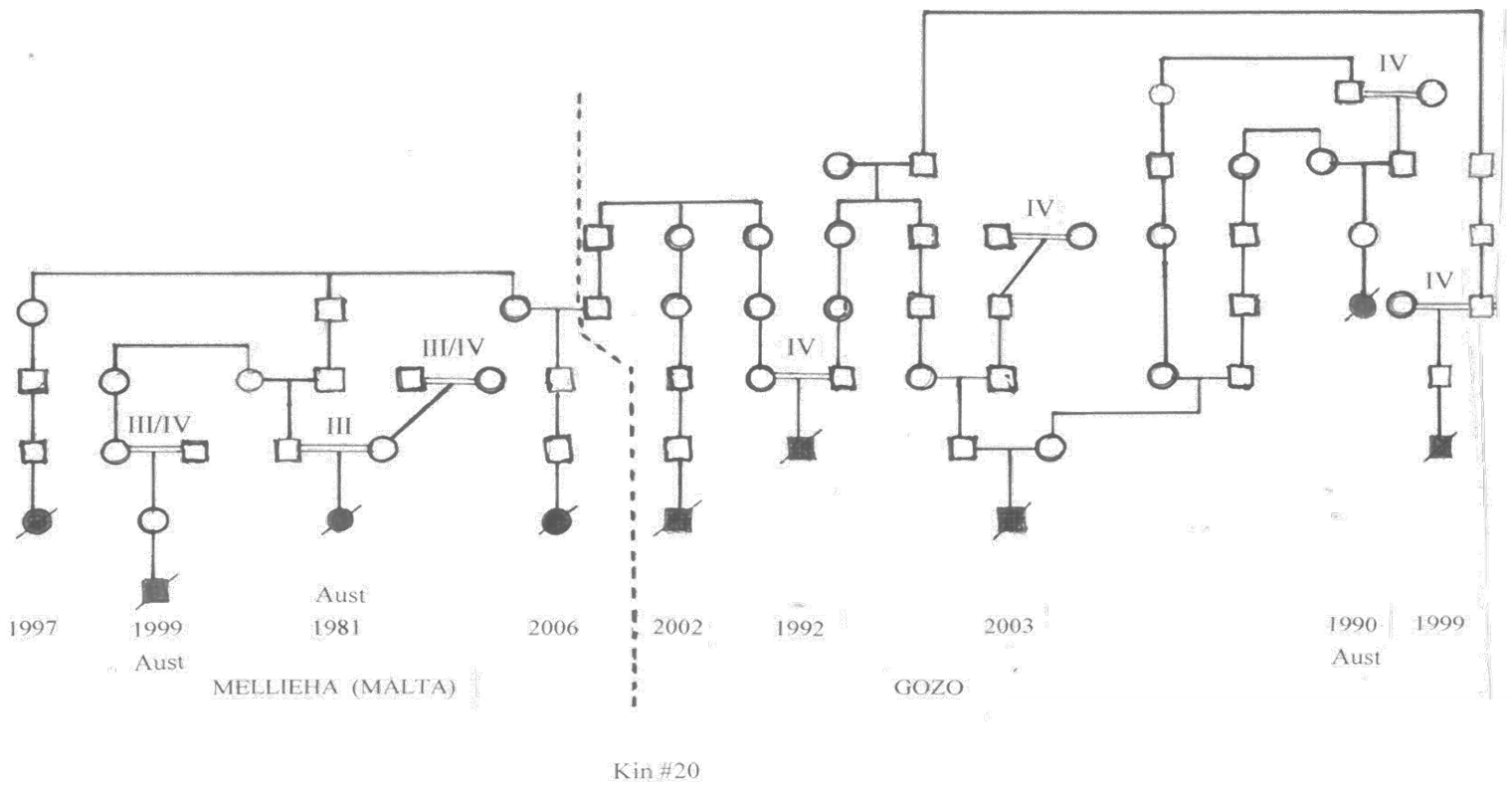
The population of Malta in 1901 was 164,952.

The next four areas were similar, with two other areas with far fewer cases. Many sporadic cases (Table 2) were widely dispersed. Kinships 5 (six cases) and 9 (two cases) were from a large village, with Kinship 17 (three cases) from and Kinship 4 (two cases) from neighbouring small villages. Nearby were Kinships 3 (four cases) and 10 (two cases) and Kinships 2 (12 cases) and 8 (two cases) at large villages.

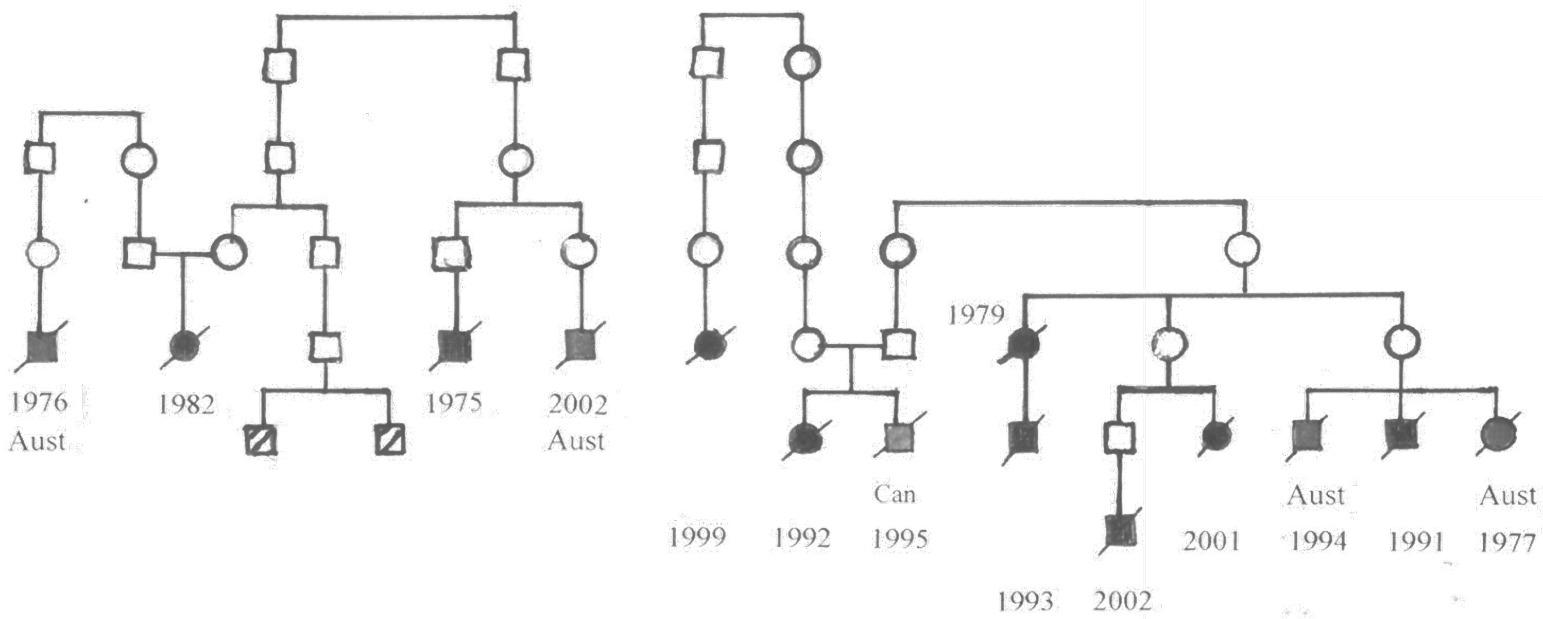
**Figure 1:** The age incidence at death of MND cases in Malta and Australia.



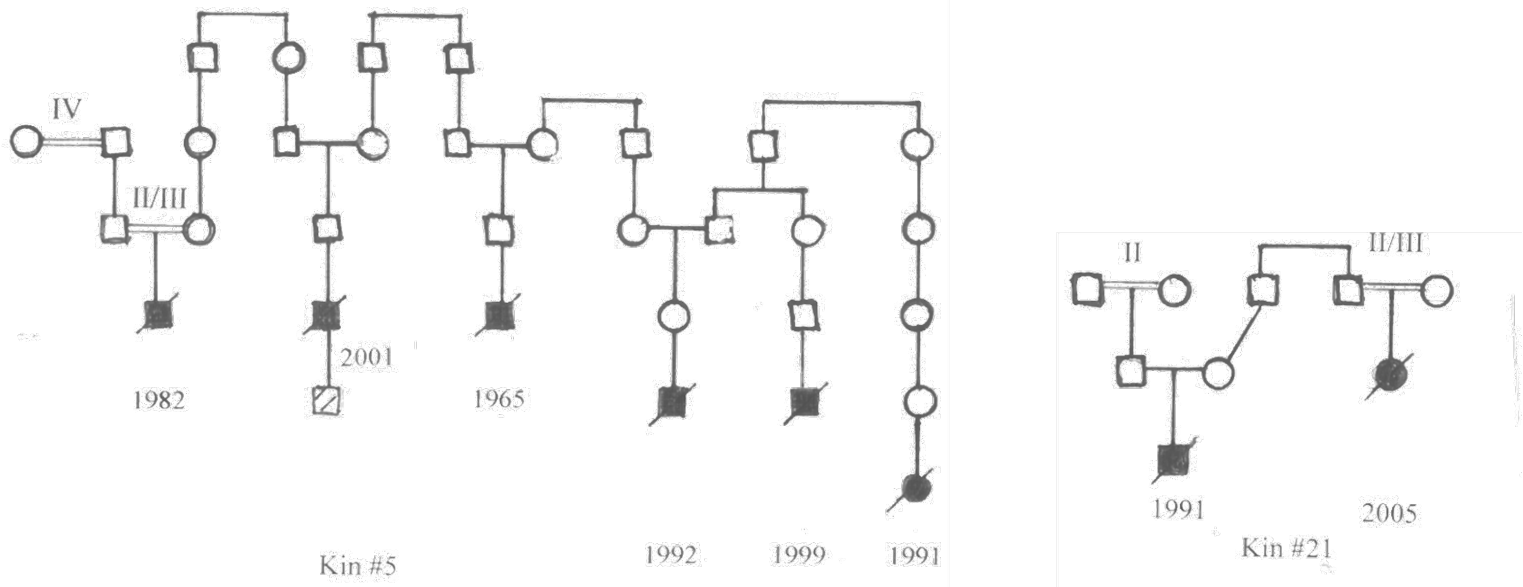
**Figure 2:** Kinship group #2. Seven and perhaps others are probably familial.



**Figure 3:** Kinship group #20 which had cases from Malta and from the island of Gozo.

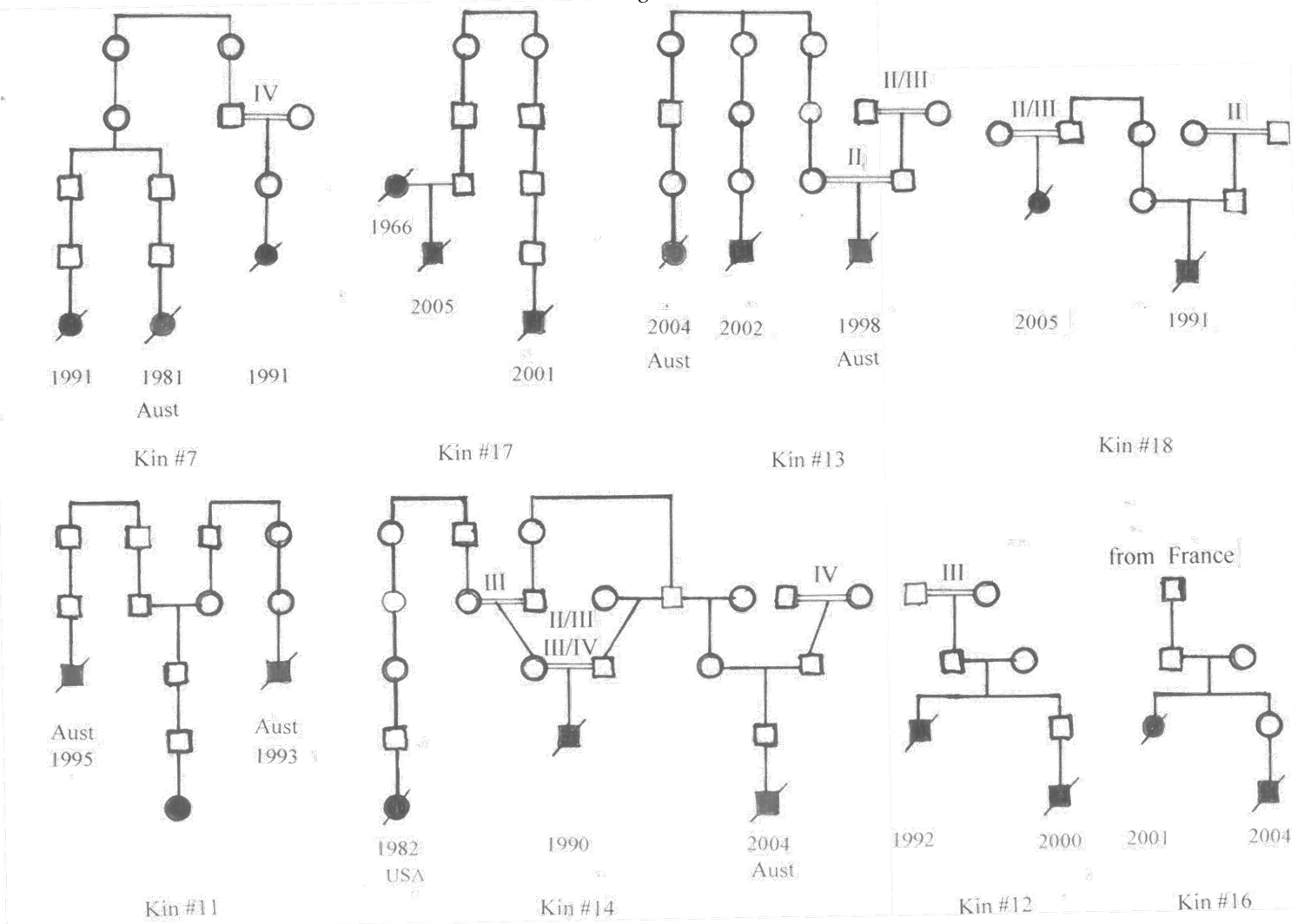


**Figure 4:** Kinship groups #3 and #1. Kinship1 on the right may be familial. The two hatched sibs were paralysed by poliomyelitis.



**Figure 5:** Kinship groups #5 and #21.

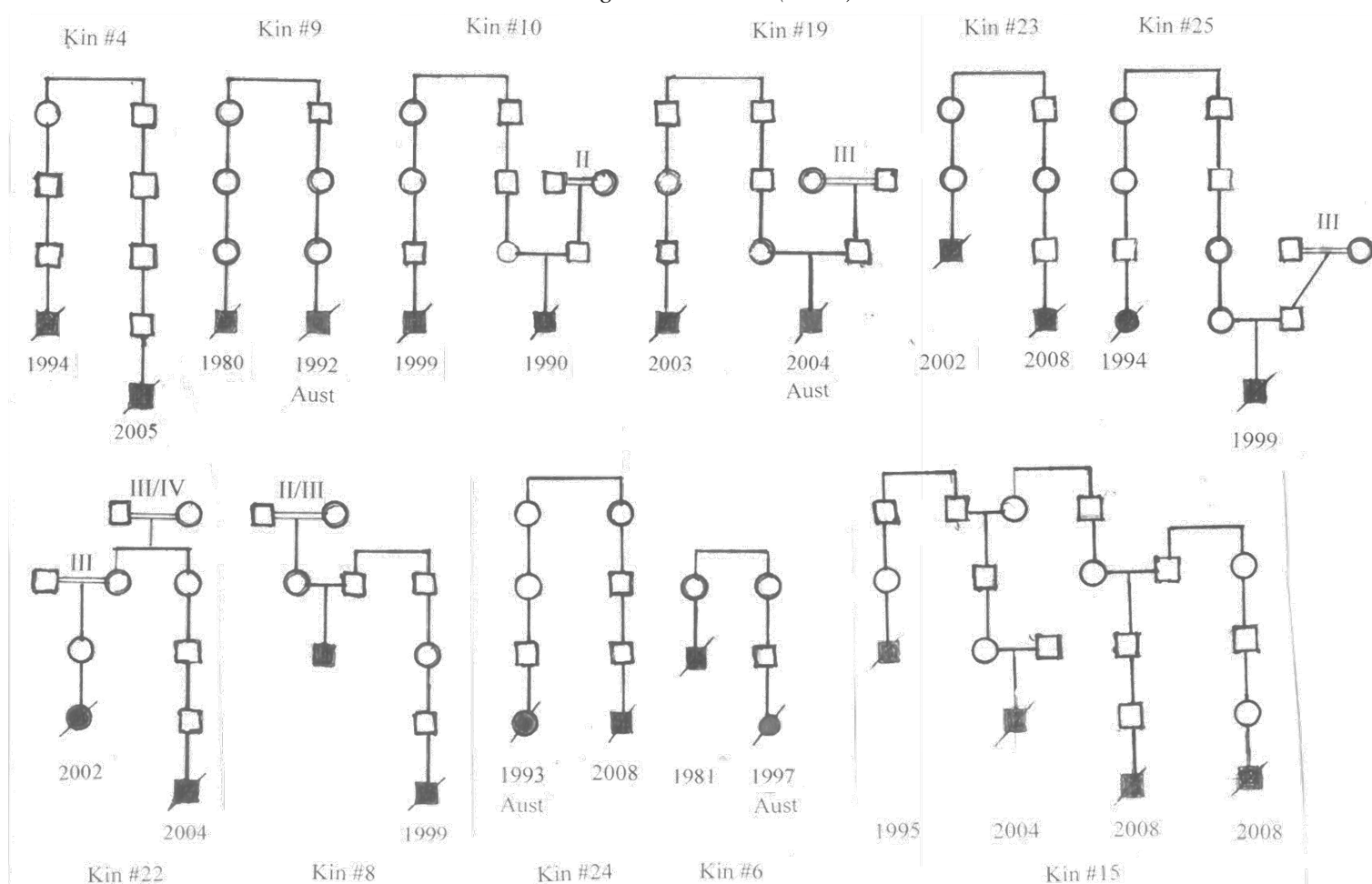
The MND who died in 2001 was the father of a boy with polio (hatched). Kinship groups with 2, 3, or 4 cases in each group. Kinship groups 8 and 11 each have a long term survivor.



**Figure 5:** Kinship groups #5 and #21.

The MND who died in 2001 was the father

of a boy with polio (hatched). Kinship groups with 2, 3, or 4 cases in each group. Kinship groups 8 and 11 each have a long term survivor. (Cont.)



**Consanguinity**

The numbers of consanguineous marriages have changed over the years, peaking at the end of the 19<sup>th</sup> century, with higher rates in Gozo. Among the MNDs, there was more than twice the proportion on Gozo than on Malta, although there was little difference in each between the two generations (Table 3). Four MNDs had multiple consanguinities of parents and grand-parents (Table 4), including two cases among Kinship 13.

**Table 3:** Consanguinity among marriages of parents and grand-parents of MNDs

	N marriages	II	II/III	III	III/IV	IV	Total
MND Parents Malta	163	4	3	1	1	3	12
Gozo	15		1			1	2
Grand-parents Malta	313	3	4	7	2	11	26
Gozo	33	1	1	2		1	5

**Table 4:** Multiple consanguinity among parents and grand-parents.

	Parents	Grand-parents	Kinship group
MND 10	II/III + III/IV	III	13
MND 149	II	II/III	13
MND 27	II/III	IV	4
MND 131	II/III	IV	

### Foreign ancestors

Some surnames suggest foreign origin eg Catania and Genovese with many others common in Italy: two cases (Kinship 15) were probably of recent Italian origin. In Kinship 16 the grandfather of the aunt and her nephew were French and the mother of a great grand-parent (case 6) was probably also. Six of these were among the linked cases. One had a Spanish mother. Three had British grand-fathers and six had British great grand-fathers (one of whom had been born in Corfu). One mother was born in Turkey of a British father and a Maltese mother from Egypt. Two cases had British fathers and another, a British mother. Of these 14, only four belonged to linked family groups (see below).

### Maltese from abroad

Five had a Maltese grand-parent from Tunisia, Benghasi, Sicily, Kephallonia or Corfu and one father was from Tunis. One father whose mother was probably Italian, was from Tripoli and the mother was probably British from Italy. One case (from Australia) was omitted: his non-Maltese father was from Sicily although his mother, from Tripoli, had a Maltese father.

### Incidence of MND

I have only 25 cases who died in Malta from 1965 to 1989. MND was rarely diagnosed or put on the death certificate until consultant neurologists were appointed. From 1990 to 2009 there were 58 686 deaths in Malta (excluding Gozo) of which 122 were MND giving an incidence of 2.1 per thousand. For New South Wales (NSW) from 1991 to 2006, there were 3 298 deaths of those born in Malta, of which nine were MND, an incidence of 2.7 per thousand. The populations were not entirely comparable: the Maltese deaths included all ages with a few foreigners, whereas the NSW deaths were mainly middle-aged males who had come to Australia as young immigrants.

### Discussion

Although ten per cent of cases are familial, the remainder are sporadic and the diagnosis with a single

name is now thought to conceal a number of different groups with different causes. Without a starting point, a priority is to find what these groups might be.<sup>2</sup> In large countries it is not easy to retrospectively survey families as many are spread over multiple boundaries. Malta, on the other hand, had a population which can be traced, but relatively few MND cases. The population was stable with some addition of foreign genes. It is not possible to find earlier MND cases as there were few hospital notes and the diagnoses will be doubtful: of the first 11 cases, five were subsequently changed on death. Several large 'villages' had no cases in this study, although several villages like B'kara and Sliema grew considerably around 1900.

The median age of death in all the groups was very similar at about 64 yr<sup>3</sup> and would seem to be lower than the ages for England and Wales (see<sup>4</sup>) and lower than the mean age of onset of 65.2 yr for males and 67.2 for females in Scotland.<sup>4</sup> The distribution of familial and other cases suggest no hot spots of special causal factors. The age of death was unchanged by emigration to new lifestyles in a different hemisphere.

The relationships of these MNDs may be due to the small population, about 250,000 in 1940, or may be more obvious than in widely dispersed populations. A marriage of cousins affects only their children, but numerous marriages with consanguinities of grand-parents and great grand-parents may have significant later effects on many children. There are several different groups: familial cases, kinship groups, sporadic cases and six with long-term survival. In other studies, from five to ten per cent of cases are familial, but in Malta may be higher.<sup>5</sup>

With the first 100 and the final 206 cases, there were similar proportions of 46 %. Whether these different Maltese groups represent different clinical entities can only be suggested from this study, which should be continued in both Malta and in Australia with genetic testing of relatives of these and new cases.

This research was approved by the Medical Ethics Committee, Malta and by the Curias of Malta and Gozo. A poster showed earlier results at an MND meeting.<sup>6</sup> The data on cards, computer print-outs and notes etc will be deposited in the Melitensis Collection of the University of Malta.

I have no interests to declare. My annual stays in Malta were funded from my pension.

### Reference

1. Strong M. ALS: one disease or many? *Amyotrophic Lateral Sclerosis* 2007; 8: 215-216.
2. Turner MR et al. Controversies and priorities in amyotrophic lateral sclerosis. *Lancet Neurol* 2013; 12: 310-322.
3. Martyn CN. Epidemiology. In *Motor neurone disease* AC Williams ed. 1994 Chapman & Hall Medical 383-426.

4. Forbes RB, Colville S, Parrott J, Swingler RJ. The incidence of motor neurone disease in Scotland. *J Neurol* 2007;254:866-869.
5. Figlewcz DA, Rouleau GA. Familial disease. In *Motor neurone disease* AC Williams ed. 1994 Chapman & Hall Medical 427-450.
6. Wyatt HV. Motor neurone disease among Maltese in Malta and Australia: many sporadic cases are related. (Abstract) *Amyotrophic Lateral Sclerosis* 2007; 8: 215-216.