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Huntington's chorea (HD) in Malta: epidemiology and origins

Since 1994 a Genetic Counselling Center devoted to assisting to subjects at risk from HD has been operative in Malta.
Data evaluated in 1994 by this Center, represents, on the whole, 23 family nuclei. Forty living subjects with HD were found (26 males and 14 females) as well as 185 subjects at risk from HD.
It appears that Malta is an HD "focus", with a disease incidence of 11.8 out of 100.000 inhabitants. This value appears to be high with respect to the world average incidence of 5.0 (Tibben, 1993) and to other values found in the Mediterranean area.
The origin of the disease on the island would appear to be "local". The founder(s) can be traced far back in time, and probably brought this disease to the island through the maritime traffic, even if the concomitance of local mutations is not excluded.

Key words: Huntington's chorea, Malta

With the present work we intend to draw the attention of human genetic studies to the HD "focus" existing in Malta. It was signalled in the past only in 1967, by a local psychiatrist named Cassar, but his suggestions, supplied to the local Authorities in order to act socially and circumscribe the development of the pathology on the island, have been unheeded for more than two decades. It is only in the last few years that the Maltese Health Department has included HD in the pathologies at high risk for the Country and authorised the project of one of the Co-authors (Prof. A. Cuschieri), local genetist at the Faculty of Medicine. His project aim is to offer specific counselling to the families affected by this neurological pathology.

Materials and methods

In 1993, at the Neurogenetic Clinic of St. Luke's Hospital in Malta, a systematic collection of the neurological cases identified in the country begun. In January 1994 a HD presymptomatic screening programme for persons at risk was started up (Mac Millan et al., 1993). In the counselling office, a geneticist and a psychologist, Dr. Buhagiar, are at work. After checking the individuals with clear signs of HD, the Counselling Center offers its services to all those at risk from the illness. The latter, after a thorough screening carried out by the geneticist, start psychological counselling, allowing them to decide if it is the case to submit themselves to specific DNA analysis that permits the eventual presence of a specific HD mutation to be revealed.

With the present paper we intend to present the results of the 1994 genetic screening program carried out by the Center for HD Genetic Counselling. More specific psychological data

(concerning the pre-sympomatic test) has been presented by another communication (Grassivaro Gallo et al., 1998).

Results

Epidemiology

In total, 23 HD family nuclei were identified, with 40 clear HD cases and 9 "doubtful" ones; the number of subjects at risk appeared to be 185 (Tab. 1). The individuals who had died from HD (notified by asking the families' components) numbered 19 in all. Among the affected subjects, a certain degree of sexual distinction was found: males 26, females 14. On 31 of these subjects the average age was also calculated: 51.19 ± 14.09 years. With respect to the local population (339.173 inhabitants - data reported by the Central Office of Statistics - 1994-, valid to January 31st, 1993), we estimated that, for HD, the prevalence on 100.000 persons is: 11.79 (Fig. 1).

Table 1: *Family nucleous, affected subjects (males, females) and at 50% risk for HD*

FAM. NUCLEOUS Nr.	SUBJECTS			
	AFFECTED Nr. M	F	TOT	PROB. AFFECTED Nr.	AT 50% RISK Nr.
1°	1	/	1	/	2
2°	/	1	1	3	6
3°	9	2	11	1	35
4°	1	1	2	/	5
5°	1	/	1	/	20
6°	1	/	1	/	7
7°	/	1	1	3	9
8°	1	1	2	/	2
9°	1	/	1	/	11
10°	2	/	2	/	3
11°	1	/	1	/	6
12°	1	1	2	/	14
13°	1	/	1	/	5
14°	2	1	3	1	12
15°	1	1	2	/	5
16°	/	/	/	/	3
17°	/	1	1	/	9
18°	1	1	2	/	10
19°	/	1	1	/	8
20°	1	/	1	/	2
21°	/	1	1	1	3
22°	/	1	1	/	8
23°	1	/	1	/	2
Tot.	26	14	40	9	185

Table 2: *HD Family Names*

FAMILY SERIAL NUMBERS	NAMES PRESENT IN NR.	FOUNDERS NR.	FAMILY SERIAL NUMBERS	NAMES PRESENT IN NR.	ALIVE AND DEAD AFFECTED NR.
1°– 9°	9	1	1°–22°	22	1
10°–12°	3	2	23°–29°	7	2
13°–14°	2	4	30°–32°	3	3
			33°–34°	2	4
			35°	1	6
Tot.	14	23		35	59

By carrying out the family anamnesis, it was possible to draw up all 23 genealogical trees: to furnish an example, here only 7 of them are reported (Graphs. 1 to 7). They correspond to the family nuclei 3°,4°,6°,9°,12°, 14°, 18° reported in Tab. 1. From the analysis of the genealogical trees, the following observations arose:

1) HD cases appear to be isolated within the family nuclei, with the exception of certain genealogical trees which had particularly elevated values in affected individuals (Graph. 1:HD3°), going back six generations and offering 11 clear cases of HD; 2) among the members of a family, the disease cannot spread for some generations (Graphs. 2 and 7: HD6° and 18°); 3) marriage among consanguineous members sometimes occurred (Graphs. 1 and 3: HD 3° and 6°); 4) in some cases, subjects at risk or affected subjects, migrated to other countries (Graphs. 2,3,4,5,6 and 7: HD 4°,6°,9°,12°,14°).

Origin

In Fig. 2 and Table 2 the results of two analyses carried out on the villages of origin and on the family names of the founders and HD affected subjects are depicted.

A) From Fig. 2 it appears that the affected centers (founders) are in both the marginal/agricultural economy and inner centers, i.e.: Rabat, Qormi, Balzan and Gharghur. It must be considered that the latter had already been mentioned by Cassar (1967) as a prevailing center for the disease, because 6 HD affected families lived in it; while the first HD case in Malta (mentioned in 1872) was found in Zurrieq, in the southern coastal region.

In the individual affected at present, HD would also have spread to the eastern harbour area of the island surrounding the capital city, La Valletta.

Both the northern area of the island and Gozo island are relatively excluded from HD, as is the southern region of Malta, whose inhabitants are mostly fishermen (village of Marsaxlokk).

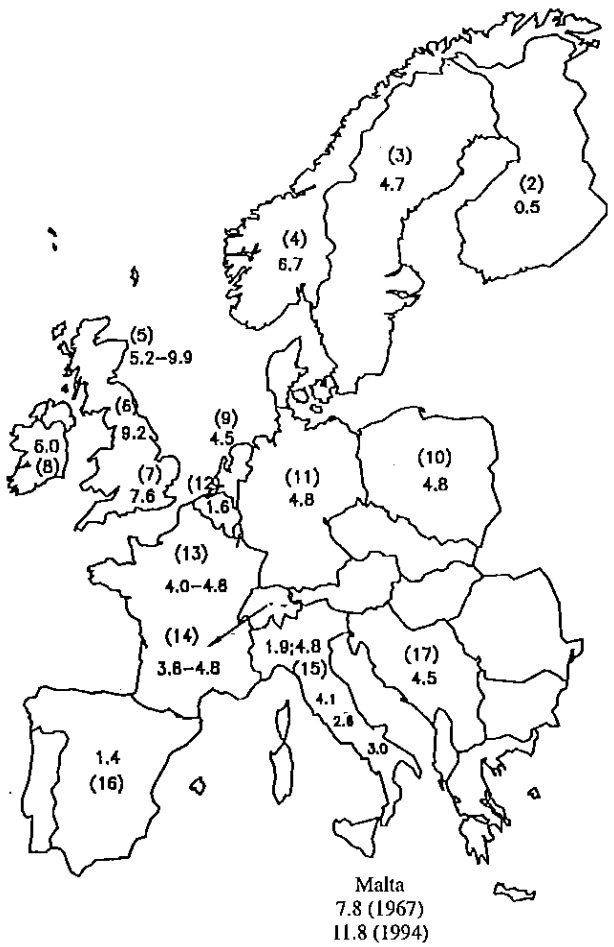
B) The survey on family names (Tab. 2) highlights that among the 23 founders it was possible to distinguish 14 different family names, characterised in this way:

1) none of them appears to be of recent British origin; 2) the 13° and 14° family names,

Figure 1: *HD prevalence in Europe*

LEGENDA

1 Iceland (Gudmundsson, 1969)
2 Finland (Palo et al., 1987)
3 Sweden (Mattsson, 1974)
4 Norway (Saugstad e Odegard, 1986)
5 Scotland (Simpson e Johnston, 1989; Bolt, 1970)
6 U.K. (Caro, 1977)
7 Wales (Walker et al., 1981)
8 Ireland (Nevin et Morrison, 1990)
9 Holland (Tibben, 1993)
10 Poland (Cendrowski, 1964)
11 Germandy (Przuntek et Steigerwald, 1987)
12 Belgium (Husquinet, 1970)
13 France (Petit, 1970; Leger et al., 1974)
14 Switzerland (Zolliker, 1949)
15 Italy (Govoni et al., 1988; Mainini et al., 1982 Frontali et al., 1990; Di Maio et al., 1992; Groppi et al., 1986)
16 Spain (Ordonez, 1970)
17 Jugoslavia (Sepcic et al., 1989)

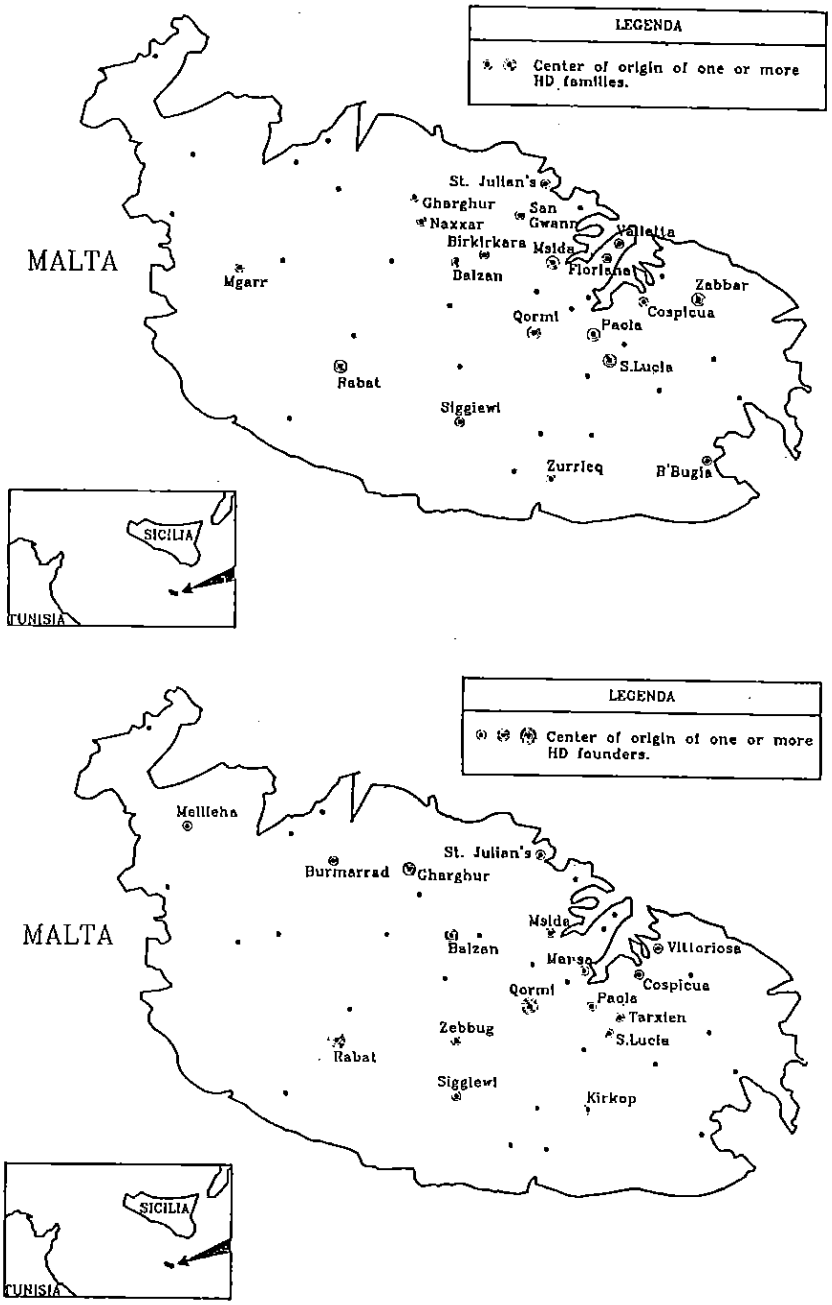


each of them found in 4 founders, are quite common in Malta; in particular: one of them was mentioned by Cassar (Personal communication, 1995) as being one of the most frequent from among the 1967 HD cases signalled; 3) the most common family names appeared at maximum in 4 founders: 4 out of 23 is a small fraction of them.

Out of a total of 59 HD subjects (both living and deceased) we found 35 different family names, among which:

1) only 4 are of recent British origin, the remaining are Maltese; 2) the 35° family name is the same as one of the most common, found in the founder; 3) 22 out of 35 is the strongest fraction of different family names, showing one affected person only.

Figure 2: *The island of Malta*



Discussion

During the first year of the HD Genetic Counselling Centre's activity, it was possible to identify 23 HD family nuclei, with 40 living cases of the disease. Obviously, the cases found are not all those to be found in Malta, but only those that emerged from the first screening.

The family trees that it was possible to draw up, have some of the well known HD characteristics, such as HD absence in some generations or the appearence of apparently isolated cases within the affected family nuclei. The relatively high incidence for males was a sexual discrimination stigmata already found in previous informal screenings (Cassar, 1967).

We would like to highlight some peculiarities reflecting certain aspects of the Maltese culture that clearly emerged during the counselling talks. Among these, a fatalistic acceptation of new HD cases arising in a family, as if they were caused by an inexorable fate or a visitation by God. Furthermore the subjects at risk decided to continue having children, without submitting themselves to the pre-symptomatic diagnosis. The second serious and hazardous aspect is due to the endogamous marriages that are frequently found in the island and that do not seem to be daunted in spite of the presence of such a serious disease. The great geographical dispersion of the Maltese HD cases due to emigration (that at present involves not only Europe but all continents), does not contribute towards diminishing the intensity of the "focus" in Malta. In fact, if the cultural spur towards an endogamic structure of the family is considered, in the perspective or in the imminence of a marriage, an immigrant returns to the island and chooses his future wife from his circle of relatives, underlining his behavior with this phrase, many times repeated: "it is much better to know your future spouse well". In fact, who can you know better than close relatives ?. Independently from marriage, many Maltese immigrants have recently returned after Malta's indipendence (Grassivaro Gallo et al., 1998).

The Maltese HD "focus" appears in all its importance from the comparison of calculated disease prevalence (11.8 on 100.000 inhabitants), not only in comparison to the world average (5.0; Tibben, 1993), but mostly to the findings of the European scenery (Fig. 1), in which no country has an HD prevalence close to the Maltese one.

Regarding the European scenery, we would like to mention two regions, connected to Malta historically because of close relationships (United Kingdom) or geographical closeness (Sicily).

As far as the United Kingdom is concerned, the prevalence value, even if relatively high, in some cases, is lower than the value of 10 (we have already pointed out that the family names connected to HD are not, usually, of British origin).

The Mediterranean basin appears to be characterised by much lower values with respect to the Maltese ones and they are distributed between the value of 1.4 (Spain); 1.9-4.8 (Italy); 4.5 (former Yugoslavia). In particular, if the island of Sicily is considered (only around 100 Kms away from Malta), no HD "focuses" have been found to date on the island; a recent survey carried out by the Palermo Epidemiological Observatory of the Sicilian Region gave negative results (Grassivaro Gallo et al.,1998). Only the Roman Centre for Genetic Counselling of the Italian Centre of Research (CNR) signalled some sporadical HD cases in the Sicilian region of Sciacca, in the Province of Agrigento (Iacopini, 1996 personal communication).

From the above outline, the Maltese HD "focus" appears to be substantially local; while its consistency appears to be substantially due to isolation and endogamy.

To formulate hypotheses on the origin of the HD "focus" in Malta, we observed the structure of the local population (Mahoney, 1995). The islands of the archipelago were inhabi-

ted until the neolithic era (5200 B.C.) and present several imposing memories of their past (i.e.: the megalithic temples). It is not easy to clarify the origin of the Maltese population, but a Phoenician group was certainly the first to settle on the islands. However, its central position in the Mediterranean basin favoured the landing of many and manifold people. On the whole, the following contributed to Maltese ethnogenesis: Phoenicians, Arabs, Romans, Italians and Sicilians, and in more recent times, the French and the British (the last people to leave the island) must be added. The traditional culture is Sicilian-Italian, but recent culture was modelled on the British matrix. The language belongs to the Semitic group, but it is strictly connected to the Arab language spoken in Tunisia. The religion, rigidly Catholic, has many ardent acolytes among the population; for this reason the Governmental position which is contrary to legalizing abortion is clearly understandable. Substantially, Malta is a melting pot of different people and different cultures. Bearing this in mind, we have attempted to formulate two hypotheses on the origin of HD in Malta.

The maps presented in Fig. 2 appear to be, on the whole, of little use to this aim. The small dimensions of the island (27 x 14 Kms) mean that the villages and hamlets cannot be isolated since they can easily be reached on foot one from the other (the average distance that could be covered during a simple walk is 16 Kms).

The above mentioned maps mostly clarify the recent history of HD in this country. From the inner and western marginal centers, in fact (where the founders lived), the disease has spread, invading the harbour trade area surrounding the Capital city (the finding of HD in the areas surrounding La Valletta bear witness to this theory).

There are some recent historical reasons that tell us why families of modest social status, formerly rural, settled in the industrial and trade area 50 years ago.

Due to the second world war events, the middle/high class population, that previously lived in the Maltese harbour trade area, moved away from it because of the bombings. At a later date, the houses, left empty, were occupied by the formerly rural population, which was less affluent and which was attracted by the prospect of an easier working opportunity in the dockyards and shipyards (Frendo, 1989).

A more probable method for clarifying the origin of HD, appears to be the analysis of family names (Table 2), which can be summarised as follows (as far as the founders are concerned): the family names are all of local origin, distributed among 23 founders bearing all the 14 family names under scrutiny for HD; only a very small fraction of them (4 out of 23) share the same family name.

Regarding present HD patients, on the other hand, the finding of Maltese family names is confirmed; to this fact we must add the presence of a very high fraction (22 out of 35) bearing different family names. These observations testify the old presence of HD "in loco".

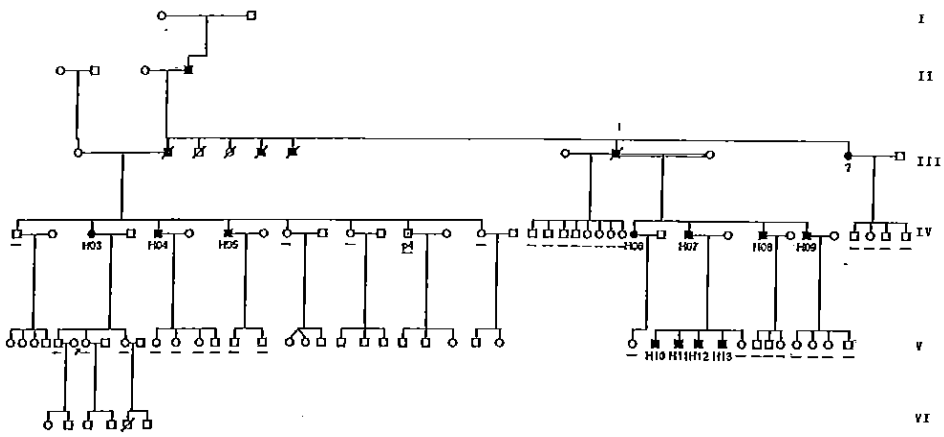
The data collected allows us to conclude as follows:

1st hypothesis: the founder (probably one) arrived in Malta presumably a very long time ago. As a consequence, the disease had all the time to spread to different families (hence different family names). As Malta is a sailing centre, it is not difficult to hypothesize that a HD affected sailor, disembarked on the island, settled there and then reproduced. The landing of an affected sailor could have happened more than once in the history of the island.

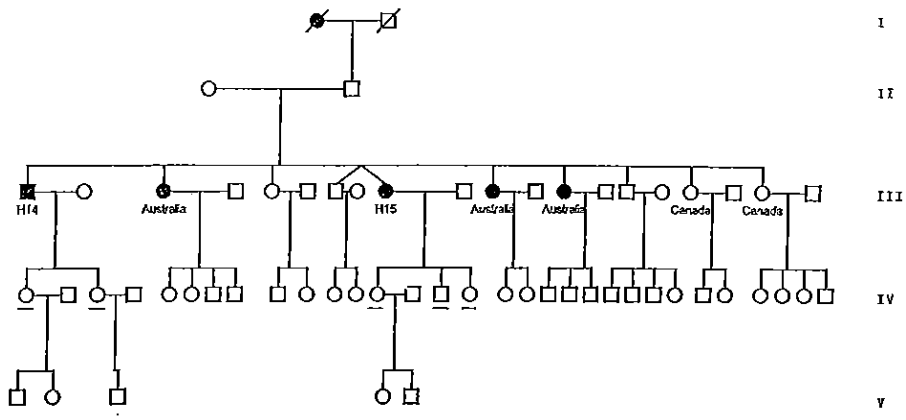
It is not possible, however, to exclude the:

2nd hypothesis: the HD founder could have been the carrier of a mutation, which had arisen in Malta, a very long time ago! Only data on the molecular structure of the mutation could highlight the origin of HD in Malta; for the moment the impossibility to perform "in loco" DNA analysis interferes with the availability of any such information.

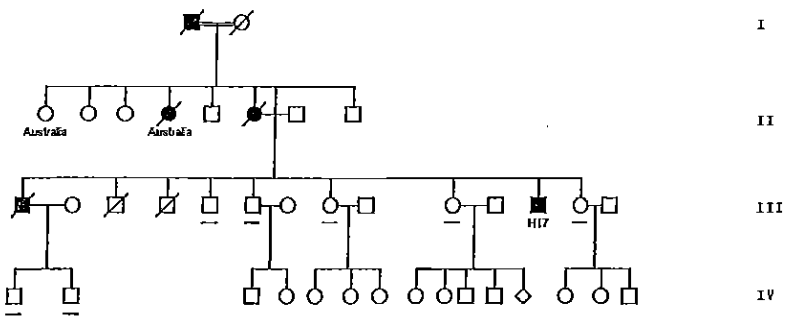
Graph. 1: *HD 3° Family tree*



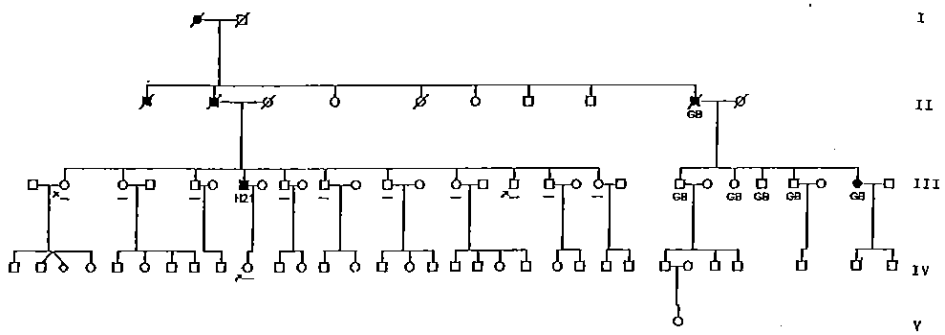
Graph. 2: *HD 4° Family tree*



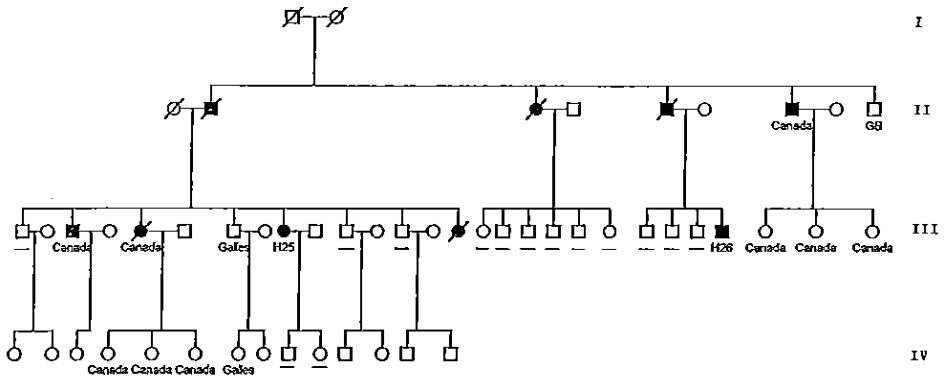
Graph. 3: *HD 6° Family tree*



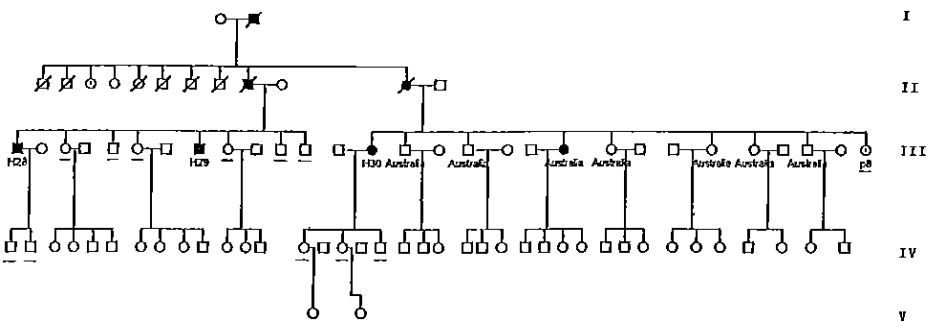
Graph. 4: *HD 9° Family tree*



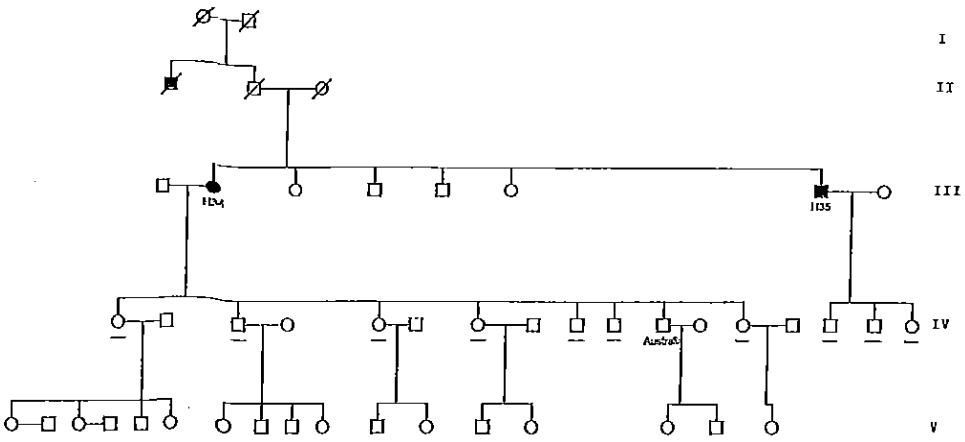
Graph. 5: *HD 12° Family tree*



Graph. 6: *HD 14° Family tree*



Graph. 7: *HD 18° Family tree*



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