ATTRv amyloidosis Italian Registry: clinical and epidemiological data

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ABSTRACT

Introduction: ATTRv amyloidosis is worldwide spread with endemic foci in Portugal and Sweden, Japan, Brazil, Maiorca, and Cyprus. A national Registry was developed to characterise the epidemiology and genotype-phenotype correlation of ATTRv amyloidosis in Italy and to allow a better planning of diagnostic and therapeutic services.

Methods: Fifteen Italian referral centres for amyloidosis spread all over the country have contributed to the Registry.

Results: Four-hundred-forty-seven subjects were enrolled, 187 asymptomatic carriers and 260 affected patients. Thirty-one different mutations were recorded. The seven most represented genetic variants were significantly different in terms of age at onset, clinical features and geographical distribution. National prevalence is 4.33/million with higher values in Southern Italy. Overall symptoms of polyneur- opathy were present at disease onset in about half of the patients, symptoms of cardiomyopathy in a quarter of patients, the rest referring carpal tunnel syndrome, dysautonomia or lumbar spinal stenosis. 52.6% of patients were in FAP stage 1, 20.4% in stage 2 and 13.5% in stage 3, while 13.5% patients had no neuropathy, presenting only cardiological symptoms.

Conclusions: We presented an epidemiological study based on collaboration among referral centres for ATTRv amyloidosis spread in all the Italian territory, using web-based Registry. It provided a detailed map of the regional distribution of the disease. The increased awareness of the disease among general practitioners and medical specialists has contributed to reduce the diagnostic delay and the rate of misdiagnosis. The Registry will allow to collect also future information about clinical and instrumental follow-up.

Abbreviations: ATTRv: Hereditary transthyretin amyloidosis; CIDP: chronic inflammatory demyelinating polyradiculoneuropathy; CTS: carpal tunnel syndrome; FAP: Familial Amyloid Polyneuropathy; LSS: lum- bar spinal stenosis; LT: Liver transplantation; TTR: transthyretin.

KEYWORDS

ATTRv; Amyloidosis;

prevalence; Italy;

polyneuropathy

Introduction

Hereditary transthyretin amyloidosis (ATTRv) is an auto- somal dominant, adult-onset progressive systemic disease predominantly involving the peripheral nervous system and the heart. It is caused by mutations in the transthyretin (TTR) gene. ATTRv amyloidosis usually presents as a pro- gressive sensorimotor polyneuropathy often associated with carpal tunnel syndrome (CTS), autonomic dysfunction including postural hypotension and gastrointestinal manifes- tations, and cardiomyopathy [l]. Occasionally the disease onset is characterised by weight loss, lumbar spinal stenosis, visual disturbances or renal dysfunction. Mutations promote proteolytic remodelling, dissociation, misfolding and aggre- gation of TTR, generating amyloid fibrils that accumulate into tissues and cause the disease [2].

ATTRv amyloidosis is considered endemic in Portugal and Sweden, with foci in Japan, Brazil, Maiorca, and Cyprus. Its global prevalence is traditionally estimated as 5,000 to 10,000, but a recently published analysis reported that it might be as high as 38,000 persons [3]. Approximately 70% of patients worldwide carry the V30M mutation (presently known as V50M according to HGVS nomenclature), with age at onset reported either before or after the age of 50 years, defining two different populations with late-onset (typical in Sweden) and early-onset pheno- type (typical in Portugal), respectively. Still unknown genetic and environmental factors may influence the clinical expres- sion and the age at onset [4].

The V30M variant seems to be the most common muta-

tion in Northern and Central Italy [5]. An independent ori- gin of the V30M mutation has been postulated comparing Italian haplotypes with those from Portuguese and Swedish

patients [6]. On the other hand, in Southern Italy E89Q, F64L and T49A are the most frequent pathogenic variants, manifesting with different characteristics with respect to age of onset, phenotype and severity of the disease [7,8]. The only ATTRv Italian epidemiological study available to date was performed in Sicily and reported a prevalence of 8.8/ 1,000,000, which is lower when compared to the endemic area in Portugal, North Sweden, Cyprus and Majorca island, but higher if compared to France and Japan [7,9-12].

Liver transplantation (LT) represented the only treatment for ATTRv amyloidosis for two decades [13]. In 2011, regu- latory agencies approved tafamidis meglumine, a small mol- ecule which stabilises the TTR tetramer, preventing its dissociation into amyloidogenic monomers and slowing the disease course [14,15]. The antisense oligonucleotide ino- tersen

and the RNAi agent patisiran are recently approved innovative drugs that inhibit hepatic TTR production through target degradation of TTR mRNA [16,17]. For all these drugs, early beginning of treatment is associated with a better outcome (18]. Therefore, reducing the diagnostic delay since the appearance of the first symptoms is now an urgent medical priority [19-21].

A national Registry, funded by Telethon Foundation, was developed to better characterise the epidemiology, genotype- phenotype correlation and regional differences of ATTRv amyloidosis in Italy. The main aims were to have a detailed knowledge of national distribution of patients and asymp- tomatic carriers and to allow a better planning of diagnostic and therapeutic services.

Materials and methods

An informatics technology platform dedicated to the ATTRv amyloidosis Registry was developed and become effective in June 2017 (22]. All Italian centres with expertise in ATTRv diagnosis and management, following the same diagnostic guidelines (23], have contributed to the Registry. They were distributed throughout the Italian national territory, 7 in North Italy, 4 in the Centre and 4 in the South (Figure 1). All fifteen centres are multidisciplinary, but 11 are coordi- nated by a neurologist, 2 by a cardiologist and 2 by an internist. During a follow-up visit, usually performed every six months, each centre informed patients with a diagnosis of ATTRv amyloidosis, independently of the clinical pheno- type, about the Italian Registry.

The minimum set of baseline demographics and clinical

data collected for each patient or asymptomatic carrier included age, sex, place of residence and place of birth, TTR gene mutation, family history. For patients, data comprised age at onset of symptoms (early when <50 years; late when 50 years), type of symptoms at presentation, time to diag- nosis, duration of illness, current clinical status, possible previous misdiagnosis, comorbidities. Familial Amyloid Polyneuropathy (FAP) stage was determined (24]: stage 1, predominantly sensory neuropathy affecting lower limbs, walk without any help; stage 2, walking difficulties, needing help for walking; stage 3, patient confined to a wheelchair. Considering only patients, the prevalence of ATTRv amyloidosis was estimated based on the population census on 1 January 2019 (prevalence day).

This study was approved by the ethics committee of the

coordinating centre and then by the local ethical committees of all the involved centres. Patients willing to participate gave a written informed consent and then registered in the web-based database, choosing the doctor authorised to fill in the clinical data. Asymptomatic carriers were also informed about the Registry; upon consent, only their demographic data were included in the database. To protect patient's privacy, each centre was allowed to review only own data; the coordinating centre was able to collect global data anonymously.

Results

Participation to the registry was proposed to all patients and carriers followed at the centres included in the study. Three patients refused participation. Four hundred forty-seven liv- ing subjects were included in the Registry at prevalence day. Among them, 260 were patients, while 187 were asymptom- atic carriers. Clinical characteristics are summarised in Table 1. Male/female ratio was 0.7/1 in asymptomatic car- riers and 2.3/1 in patients. We report 163 (62.7%) probands, while the remaining 97 patients (37.3%) had a positive fam- ily history for ATTRv amyloidosis. Six patients were born abroad but resident in Italy; their ancestry was French, Brazilian, Nigerian, Eritrean, Macedonian and Vietnamese, respectively.

According to the Italian region of birth, ATTRv amyloid-

osis was more prevalent in Southern Italy, with a high range of regional prevalence up to 9.2 and 9.3/million in Calabria and Sicily, respectively, and a global prevalence of 4.33/mil- lion (Figure 1). A late-onset disease was registered in 216 patients (83.1%).

Thirty-one different mutations were recorded (Supplementary data 1). V30M is the third most frequent mutation when asymptomatic carriers are included, 90/447 (20.1%), while it is the most common mutation, 60/260 (23%), in patients. Among V30M patients, the majority

(n = 48, 80%) had a late disease onset, vs 12 (20%) present-

ing with early onset. The average diagnostic delay was

2.58 years (3.4 years in probands, and 1.2 years in patients with positive family history). The seven most common mutations were significantly different in terms of age at onset, clinical features and geographical distribution accord- ing to the birthplace (Table 1, Supplementary data 2). Two of the six patients born abroad carried mutations that were not found in patients with Italian ancestry. A French patient carried the S77T mutation and a Vietnamese the A97S mutation. In both cases, the phenotype is consistent with previous reports (25,26]. The other four patients carried V30M (three cases) and E89Q (one).

Overall symptoms of sensory and/or motor polyneurop- athy were present at disease onset in 124/260 patients (47.7%), symptoms of cardiomyopathy in 67/260 (25.8%), and symptoms of dysautonomia in 9/260 (3.5%). CTS was diagnosed at onset in 21/260 patients (8.1%). Onset with a combination of neuropathic, cardiologic and dysautonomic symptoms was found in 39/260 (15%). Table 1 also summa- rises the genotype-phenotype correlations.

Forty-eight patients (18.5%) received a misdiagnosis. All of them were probands, i.e., 48/163 (29.4%). The most fre- quent misdiagnosis reported was chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in 25 patients. Other diagnoses were hypertrophic cardiomyopathy in 6, AL amyloidosis in 5, fibromyalgia in 2, motor neuron disease in 2, coronary artery disease in 2, hypertensive car- diomyopathy in 1, aortic stenosis in 1, vascular encephalop- athy in 1, combined adrenal cortical insufficiency and gonadal insufficiency in 1, diverticulitis in 1, hereditary neuropathy with liability to pressure palsies in 1. Diagnosis of lumbar spinal stenosis (LSS) was a cause of diagnostic delay in sixteen additional patients.

Tafamidis meglumine 20 mg daily was the treatment option in the vast majority of patients, 146/260 (56.1%). Other treatments were diflunisal 18/260 (6.9%), LT 14/260 (5.4%), combined

heart-LT 3/260 (1.2%) and doxycycline plus ursodeoxycholic acid 1/260 (0.4%). Eighteen patients were included in clinical trials (6.9%), while 70 (26.9%) patients were taking only symptomatic drugs and/or waiting to start treatment.

Discussion

Italian ATTRv prevalence

The Italian Registry for ATTRv amyloidosis involved all expert centres in the country, most likely including all patients diagnosed in Italy with ATTRv. So far, a single region, Sicily, was investigated showing a prevalence of 8.8/ million [8]. Extending this prevalence to the entire Italian population, an estimated number of 500-600 patients has been postulated (3,5]. In the present survey, the national prevalence of ATTRv amyloidosis was 4.3/million, with quite variable regional differences. The prevalence is similar to that found in France (3-4/million) [11] (David Adams, personal communication) in Bulgaria (6.2/million) and Netherlands (2.6/million) [3]. However, some considerations suggest that the Italian prevalence might be even higher: (i) the high number of unrelated patients (163 probands out of 260 patients) makes it likely that paucisymptomatic relatives of these may escape medical attention; (ii) participation to the Registry is on a volunteer basis, therefore some patients might not have been included; (iii) some Italian regions have no referral centres. Apart from some small regions, which however are close to referral centres in nearby regions, this is true for Sardinia island, with 1.6 million of inhabitants and no ATTRv patient so far diagnosed.

Despite the similarity in prevalence as well as in number

of different mutations (29 vs 31) in France and Italy, in France the most prevalent mutation, V30M, represents 62.7% of all the cases, probably because of migration from Portugal, whereas in Italy a more homogeneous distribution was observed with 1681 being the most diffuse mutation carried by 22.4% of the subjects, taking together patients and asymptomatic carriers (11].

Considering the seven most common variants, four (V30M, 1681, F64L and Vl22I) are not restricted to a unique geographic area. They could have an ancient origin, for example, 850-900 years for V30M or alternatively differ- ent foci [6]. Conversely, patients with T49A, E89Q and Y78F mutations seem to have a clear common ancestry, respectively, from Agrigento (Sicily), Syracuse (Sicily) and Bergamo (Lombardy). Haplotype studies are needed to answer these questions.

Genotype-phenotype correlations

The age at onset of ATTRV30M amyloidosis in Italy is rela- tively high (58.9 years) with only 12/60 patients (20%) show- ing an early onset. This distribution is similar to Sweden, and other non-endemic countries such as Germany, Netherlands and France [5,10].

V30M is the most frequent mutation in Italy, being car- ried by almost one-fourth of patients. ATTRV30M amyloid- osis is mainly characterised by a sensory polyneuropathy with a late onset (mean: 63.7years; range: 50-81) in most patients. During its course, the disease shows a mixed phenotype including heart and autonomic involvement, con- firming the typical phenotype found in other non-endemic areas and in Sweden [9,12,25]. Males are more frequently affected, three times more than females, very similar to the ratio of the entire cohort (2.3/1).

In this series, 1681 patients show the shortest disease dur- ation. These data are probably due to the natural history of this variant that is characterised by fast course and high mortality (41% at 3years and 63% at 5years) [27]. The per- centage of patients carrying the two cardiological mutations (1681 and Vl221) is higher than that recorded in the past in Italy and in other Western Europe countries [5]. An increased awareness of the disease among cardiologists in the last few years might in part explain this finding. Moreover, the two mutations are common in two regions of central Italy, where two cardiologic referral centres are located.

ATTRV122I amyloidosis seems to show two different phenotypes: the largest number of patients, originating from Tuscany, have the classic cardiological phenotype that resembles ATTRl68L amyloidosis. Differently, an already described patient from Sicily [28] and another from Apulia had symptoms of peripheral neuropathy without cardiac involvement.

ATTRE89Q amyloidosis is one of the most aggressive variants with onset around the age of fifty. The disease starts usually with neuropathic symptoms, but heart dys- function with heart failure and sudden death are major clin- ical issues during the disease course and in the late stage [8]. Patients have the shortest delay between symptoms onset and diagnosis, probably for the well-known geograph- ical distribution of this mutation, but also because CTS, car- diac dysfunction and peripheral neuropathy often advance in parallel, making the diagnosis more straightforward fol- lowing diagnostic algorithms proposed in the recent years [29].

In the Italian Registry, ATTRF64L amyloidosis is the second most frequent variant. It is the most common in Southern Italy, especially in Apulia and Calabria. Considering the high number of people emigrated from Southern Italy since the late nineteenth century, it is reason- able that this mutation is scattered worldwide. Indeed, the mutation was firstly described in an American patient of Italian ancestry [7]. Patients usually have a late onset. This variant, and the other mainly neuropathic variant Y78F, are characterised by a high number of sporadic patients and a long diagnostic delay. Interestingly, these two mutations are similar also for the high male/female ratio. In both cases, the clinical feature includes distal paraesthesias/CTS at onset and could be easily underestimated or misdiagnosed with other peripheral neuropathies [7,30,31].

ATTRT49A amyloidosis is probably the most peculiar in the Italian Registry. These patients present with early disease onset in 80% of cases, there is no difference in male/female prevalence and autonomic disturbances are remarkable. Indeed, orthostatic hypotension may be the inaugural symp- tom that remains isolated for many years [32]. In line with the young age at onset in these patients, all have a positive family history, the oldest onset being

at age of 55years and the oldest asymptomatic carrier being 47-year-old. Moreover, all adult family members have been genotyped and therefore, the penetrance of ATTRT49A amyloidosis was 100% at the age of 56.

Misdiagnosis and diagnostic delay

The number of sporadic cases in this series is the highest reported in a large cohort, as only about one-third of the patients had a positive family history. This number is prob- ably due to the advanced age at onset, that is the highest so far reported [5].

Lack of family history, the high number of late-onset patients and the complexity of clinical presentation are the cause of misdiagnosis reported in one-fifth of patients enrolled into our Registry. However, in other series of patients from non-endemic areas, the percentages of mis- diagnosis have been higher, reaching the 68% in the US [33]. Probably, the high frequency of mutations with cardiac manifestation that are less commonly associated with mis-diagnosis may have contributed to these data [21,34]. On the other hand, the lowest reported percentage (7.6%) of misdiagnosis is in early-onset patients in an endemic area as Portugal [35].

We have considered CTS retrospectively as the onset in patients who showed other signs or symptoms of the disease subsequently. LSS was considered neither as the onset of ATTRv amyloidosis, nor a misdiagnosis given the growing finding of local amyloid accumulation since the early disease stage [36,37]. As observed in other reports, the most fre- quent misdiagnosis was CIDP followed by hypertrophic car- diomyopathy and AL amyloidosis [20,21]. The two cases misdiagnosed as motor neuron disease were wrongly diag- nosed as a pure lower motor neuron disease rather than an upper limb onset or a bulbar onset of amyotrophic lateral sclerosis [34,38,39].

The diagnostic delay in probands was still high (3.4 years), whereas patients with a positive family history had a rapid diagnosis in 1.2 years. However, the overall delay is 2.58 years that is considerably less than what observed in the past [19,20]. Different reasons could explain this finding. First, in the last years, carriers frequently underwent periodic neurological, cardiological and other diagnostic tests, when they are in a 'high-risk age'. In these patients, instrumental signs of amyloidosis are often present before symptoms onset, and so there is no diagnostic delay. Secondly, in Italy the awareness of the disease in the last few years has dramatically increased. New treatments, the effort of medical associations together with pharmaceutical companies to spread the knowledge of the disease among general neurologists, cardiologists and general practitioners and specialists have probably contributed to this result.

Conclusion

This the first epidemiological Italian study based on a col- laboration among referral centres for ATTRv spread in all the national territory. Using a web-based Registry, it pro- vided a detailed map of the regional distribution of the dis- ease. Despite the high number of different

mutations with several phenotypes, the increased awareness of the disease among general practitioners and medical specialists has con- tributed to reducing the diagnostic delay and the rate of misdiagnosis. The Italian Registry will allow to collect also future information about clinical and instrumental follow- up, providing real-world evidence on how the new available therapies will change the history of the disease in the com- ing years, especially in the numerous non-V30M patients, who characterise the Italian cohort.

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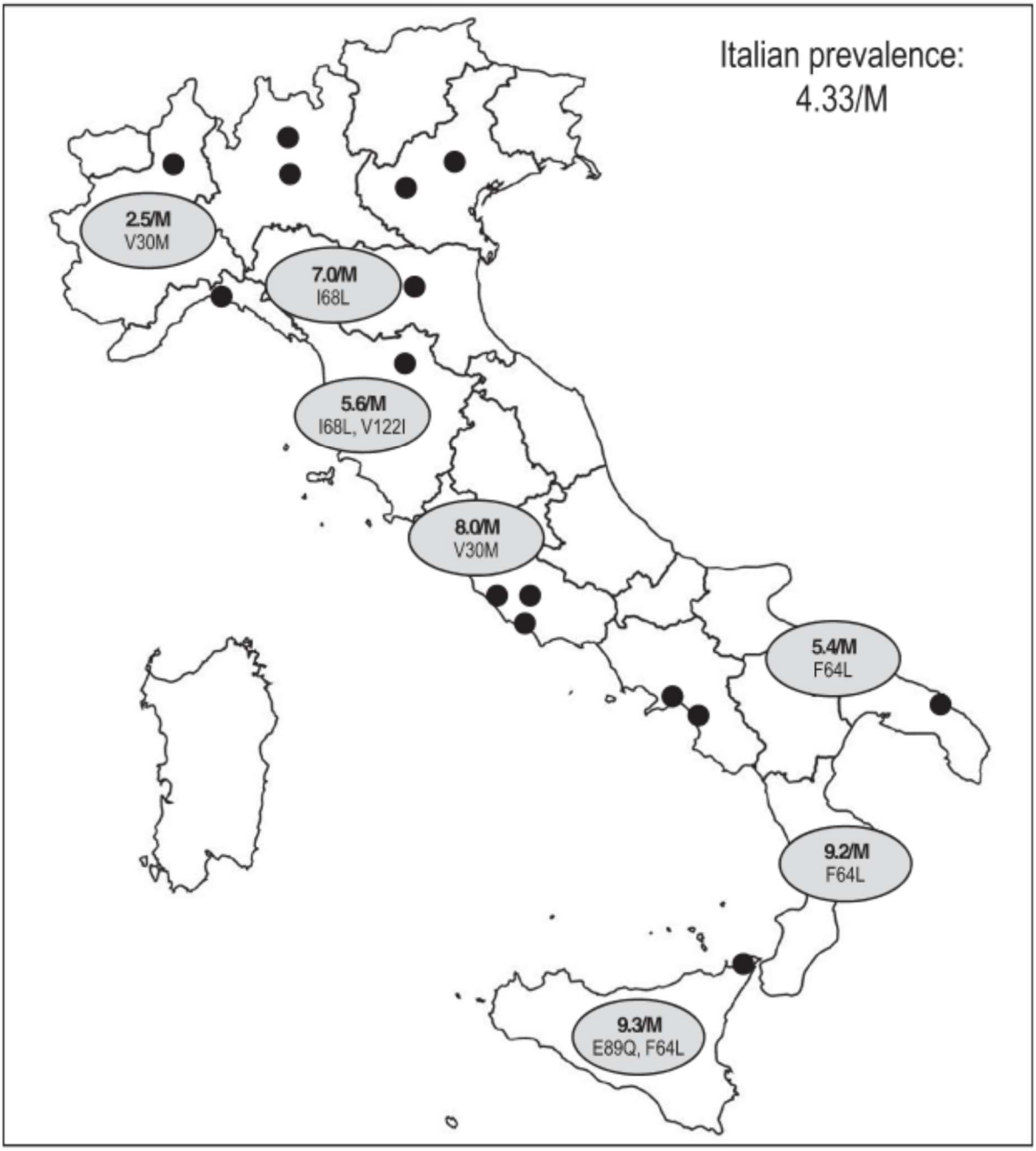

Figure 1. Prevalence (no. of patients/million) and more common mutations in the Italian regions with at least 10 affected patients each. Black circles indicate referral centres

Table 1. Clinical characteristics.

	Total	I68L	F64L	V30M	E89Q	V122I	Y78F	T49A
Number of symptomatic patients	260	47	58	60	33	13	13	10
%	100	18.1	22.3	23.1	12.7	5.0	5.0	3.5
Male/female ratio	2.3/1	2.6/1	3.8/1	3/1	1.3/1	3.3/1	12/1	0.8/1
Mean age (years)	67.1	72.4	70.2	66.2	58.5	73.7	72.6	49.4
Age range (yrs)	30–87	56–82	44–86	44–87	43–79	64–87	61–87	30–64
Mean age at the onset (years)	60.3	67.9	63.7	58.9	50.5	67.5	64.1	43.9
Age range at the onset (years)	29–82	47–79	42–80	31–81	37–70	56–82	55–81	30–55
Number of late onset (≥50 years)	216	45	56	48	18	13	13	2
%	83.1	95.7	96.6	80	54,5	100	100	20.0
Disease duration (mean ± SD; years)	6.8 ± 4.7	4.5 ± 2.4	6.5 ± 4.4	7.2 ± 5.2	8.0 ± 4.4	6.2 ± 4.2	8.5 ± 5.0	5.5 ± 3.4
Probands	163	31	42	42	11	12	10	0
Mean age at diagnosis in probands (years)	66.4	69.8	65.7	62.6	55.0	71.5	70.0	NA
Duration of symptoms at diagnosis in probands (years)	3.4	3.3	3.8	3.2	2.3	3	3.9	N.A.
Mean age at diagnosis in non-probands (years)	56.3	67.4	58.7	59.2	50.7	63	63.3	43.9
Duration of symptoms at diagnosis in non-probands (years)	1.2	0.6	1.3	1.4	1.3	0.5	6.0	0
Prevalent phenotype at onset	P	C	P	P	P	C	P	DYS
Most frequent onset symptom		Dyspnea	Paresthesia in LL	Paresthesia in LL	CTS	Dyspnea	Paresthesia in LL	Weightloss
Phenotype at prevalence day		P+ C+++ Dys +	P+++ C+ Dys +	P+++ C+ Dys +	P++ C++ Dys ++	P++ C+++ Dys +	P+++ C+ Dys +	P++ C++ Dys +++
Only heart involvement	35 (13.5%)							
FAP stage 1	137 (52.6%)							
FAP stage 2	53 (20.4%)							
FAP stage 3	35 (13.5%)							
Italian region of birth with highest prevalence	Sicily	Emilia Romagna	Apulia	Lazio	Sicily	Tuscany	Lombardy	Sicily
Number of asymptomatic carriers	187	53	33	30	19	21	3	3
%	100	28.3	17.6	16.0	10.1	11.2	1.6	1.6
Male/female ratio	0.7/1	1.1/1	0.7/1	0.7/1	0.7/1	0.4/1	0/1	0.5/1
Mean age (years)	52.3	54.8	56.8	48.3	46.2	55.7	53.3	40.0
Age range (years)	24–89	24–89	37–85	26–69	27–64	37–83	50–59	35–47

P: sensory-motor polyneuropathy; C: cardiomyopathy; DYS: dysautonomia; LL: lower limbs; +: mild (not clinically significant); ++: moderate (clinically relevant); +++: severe (clinically predominant); NA: not applicable.