



Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP

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Purpose of review

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a highly disabling, life-threatening disease characterized by progressive sensorimotor and autonomic neuropathy. The profile of the disease across Europe is inadequately understood at present.

Recent findings

The incidence and clinical presentation of TTR-FAP varies widely within Europe, with early and late-onset disease subtypes. In those regions in which the disease is endemic (Portugal, Sweden, Cyprus, and Majorca), a Val30Met substitution in the *TTR* gene is the predominant genetic cause, whereas in the rest of Europe, cases of TTR-FAP are mainly sporadic with genetic heterogeneity. Current management strategies lack cohesion and patients can experience years of misdiagnosis and suboptimal treatment.

Summary

The article aims to disseminate the findings and recommendations from two recent meetings of the European Network for TTR-FAP (ATTReuNET), a panel comprising representatives from 10 European countries (Bulgaria, Cyprus, France, Germany, Italy, the Netherlands, Portugal, Spain, Sweden, and Turkey) with expertise in the diagnosis and management of TTR-FAP. We explore the epidemiology and genetic mark of TTR-FAP across Europe and assess current management strategies, with a view to developing an alternative framework – a networked approach to disease management with an emphasis on collaboration and sharing of best practice.

Keywords

amyloidosis, epidemiology, Europe, polyneuropathy, transthyretin familial amyloid polyneuropathy

INTRODUCTION

Amyloid neuropathies are severe and life-threatening illnesses characterized by endoneurial amyloid deposits [1,2]. As a rare disease, the European prevalence of amyloidosis (including secondary amyloidosis) was estimated at 47/100 000 in 2014 [3]. Transthyretin familial amyloid polyneuropathy (TTR-FAP), also known as transthyretin (TTR) amyloidosis, is the most common form of amyloid neuropathy [1]. It is characterized by the extracellular deposition of amyloid fibrils composed of TTR, a 127 amino acid plasma transport protein for thyroxine and vitamin A that is produced predominantly by the liver [4,5].

Clinically, TTR-FAP manifests as progressive and irreversible sensorimotor and autonomic neuropathy

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KEY POINTS

- TTR-FAP is a highly disabling form of progressive sensorimotor and autonomic neuropathy, is life-threatening, and exhibits genetic and phenotypic heterogeneity within Europe.
- Variable clinical features, lack of awareness among physicians, and limited access to genetic screening can all contribute to high rates of misdiagnosis and poorer patient outcomes.
- National Reference Centres are a means to ensure early and appropriate diagnosis, treatment, and care, and to eliminate regional disparities in treatment approaches.
- ATTReuNET is a collaborative pan-European network approach to the management of TTR-FAP, aiming to help raise disease awareness, improve access to services, and guide public health policy to improve knowledge on the epidemiology in Europe.

[6], starting typically with sensory disturbances in the toes and moving rapidly upward to more proximal parts of the legs. By the time the knees are reached, the hands have usually become involved [6]. The natural course of TTR-FAP can be classified into three stages: I (sensory polyneuropathy), II (progressive walking disability), and III (wheelchair bound or bedridden) [7], with a life expectancy ranging from 7.3 to 11 years from onset [8,9].

The European Commission recommends that all European Union (EU) member countries have strategic plans in place for responding to rare diseases. This European Project for Rare Diseases National Plans Development (EUROPLAN) initiative acknowledges the importance of access to high-quality care for patients with rare diseases, and recognizes shortcomings in the existing management frameworks of many European countries [10]. The implementation of rare disease plans for TTR-FAP is not yet available across all of Europe. With this in mind, we established the European Network for TTR-FAP (ATTReuNET), comprising 15 experts for TTR-FAP from 10 European countries (Bulgaria, Cyprus, France, Germany, Italy, the Netherlands, Portugal, Spain, Sweden, and Turkey), including nine National Reference Centres (NRCs: highly specialized hospital and university teams distributed throughout the country). The panel met in November 2012 and March 2014 to share their collective experience regarding the current epidemiology, diagnosis, and management of TTR-FAP. Data were collected through the use of a semistructured questionnaire and the major findings

were assimilated into the current supplement (see Table S1 within Supplementary Materials for full questionnaire, <http://links.lww.com/CONR/A37>).

The article discusses pan-European differences in the epidemiology and clinical presentation of TTR-FAP and highlights shortcomings of current management approaches. By proposing a framework for the development of clinical networks across European healthcare systems, we hope to facilitate communication, foster collaboration, and, ultimately, offer patients with TTR-FAP, regardless of nationality, a standardized and effective management strategy.

METHODOLOGY

This article is based on data derived from two sources: a systematic literature review, and outcomes from roundtable meetings of the ATTReuNET that took place in November 2012 and March 2014. The aim of the current article, together with the other two within this series, is to disseminate the major findings from the meetings and to align these with data available from the published literature base.

Prior to the meeting in March 2014, 15 members representing 10 European countries from the ATTReuNET completed a semistructured questionnaire. The responses were used to guide the live discussion, with a focus on five main areas: epidemiology and local structure of care; diagnosis; management and funding; follow-up care of both patients and asymptomatic carriers; and the overall patient experience. The overarching objective of the meetings was to achieve a first consensus regarding the current epidemiology and genetic basis of TTR-FAP, to identify the limitations of existing diagnostic and treatment approaches and to propose alternative management strategies.

Electronic database searches (NCBI PubMed) formed the basis of the literature search within the time frame (1952 to December 2014). Key search terms included 'transthyretin familial amyloid polyneuropathy,' 'familial amyloid polyneuropathy,' 'transthyretin amyloidosis,' 'TTR-FAP,' 'TTR-FAP and Europe,' and 'TTR-FAP and Bulgaria/Cyprus/France/Germany/Italy/the Netherlands/Portugal/Spain/Sweden/Turkey'.

The history of transthyretin familial amyloid polyneuropathy within Europe

The first cases of familial amyloid polyneuropathy (FAP) were described in northern Portugal in 1952 [11[¶]], and by 1994, 1233 cases had been diagnosed at the Centro de Estudos de Paramiloidose in Porto

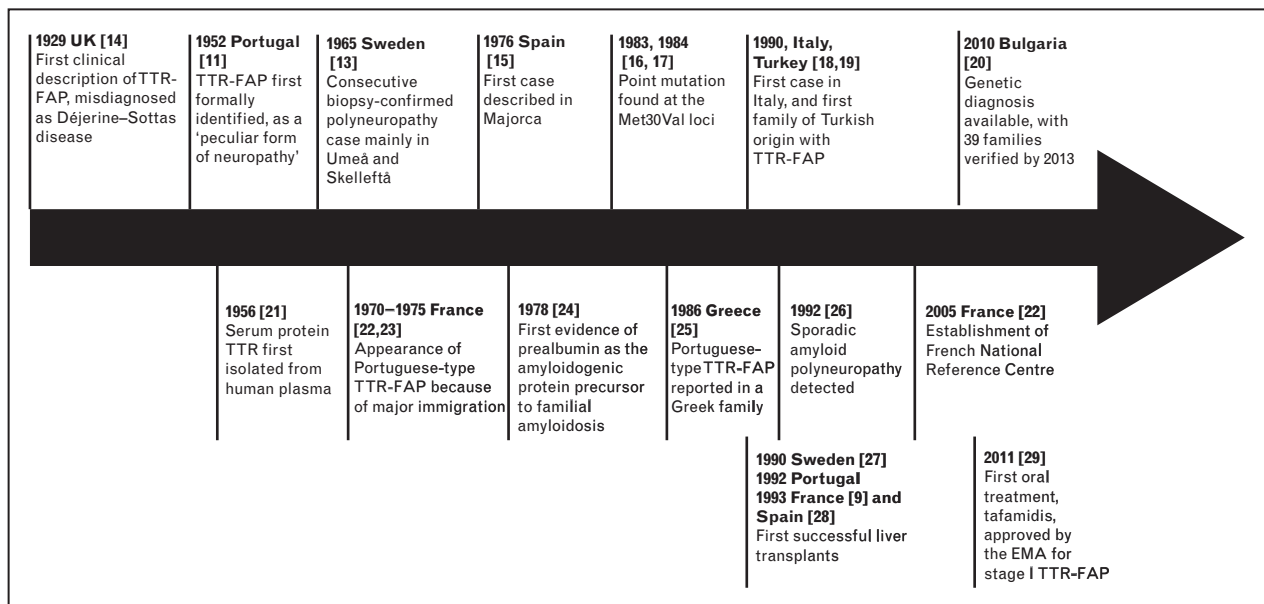


FIGURE 1. Timeline of important milestones in the European history of TTR-FAP. EMA, European Medicines Agency; TTR, transthyretin; TTR-FAP, transthyretin familial amyloid polyneuropathy.

[12]; Sweden recorded its first case of TTR-FAP in 1965 [13].

Figure 1 shows the timeline of important milestones in the European history of TTR-FAP [9,11[■],13–29]. Europe can be regarded as a pioneer in the field, given that as a continent it is credited with the introduction of genetic screening for TTR-FAP and the approval of the first oral treatment for the disease in 2011 [29]. Furthermore, the first NRC for FAP was established in France in 2005 [22].

The prevalence and genetic basis of transthyretin familial amyloid polyneuropathy in Europe

Within Europe, the incidence of TTR-FAP is highly variable. There are large areas in Portugal and Sweden in which the disease is endemic, that is, localized to one small area, with a traceable family history with a single genetic mutation [2,30[■]]. Smaller endemic foci have been identified in Cyprus and Majorca [31,32]. In the rest of Europe, cases of TTR-FAP are mainly sporadic or scattered, with no common genetic cause [22,26,33]. However, recently, an increasing number of TTR-FAP cases have been reported in Germany, Bulgaria, and Turkey.

Prevalence

In particular regions of Portugal and Sweden where TTR-FAP is endemic, disease prevalence ranges from 1 in 1000 to 1 in 10 000 people [34,35]. In 2003, the prevalence of FAP in Cyprus was 3.72/100 000 people, while the incidence was estimated at

0.69/100 000/year [32]. Using data derived from the ATTRuNET questionnaire, we observed that Portugal has the highest number of diagnosed, symptomatic cases (~2000) and more than 500 diagnosed asymptomatic carriers of the disease (Table 1). The gene carrier frequency for methionine-for-valine substitution at position 30 (Val30Met) in the northern parts of Sweden has been recently estimated at 2% in the endemic areas of Västerbotten (i.e. ~700 carrier individuals) [38]. However, the low penetrance of the trait and the often late onset of symptoms lead to a lower prevalence of the disease [39].

Beyond these endemic regions, the incidence of TTR-FAP is much lower, and there are no published estimates for prevalence rates across Europe. Of the nonendemic regions, France, Italy, and Germany have the most confirmed cases of TTR-FAP. A prevalence of 8.8/1 000 000 has been reported in Sicily [40].

Genetics

FAP is transmitted as an autosomal dominant trait arising from mutations of the *TTR* gene [4,5,30[■]]. TTR-FAP has both genotypic and phenotypic heterogeneity [2,4], with more than 100 different mutations identified [41[■]]. The nature of the mutation impacts greatly on patient outcomes, with different mutations ascribed varying patterns of clinical presentation, age of onset, and disease progression.

The most common mutation, first identified in the 1980s, is a Val30Met in the amyloid fibril protein [42]. The Val30Met point mutation

Table 1. National prevalence of transthyretin familial amyloid polyneuropathy across Europe

	Total population (millions) [36]	Surface area (thousands, km ²) [36]	Number of diagnosed, symptomatic TTR-FAP cases	Number of asymptomatic carriers of TTR gene mutation	Age range of patient cohort (years)
Portugal	10.4	92.2	2000	>500	18–87 (most <50)
Sweden	9.6	438.6	250	Estimated 7500 in clustering area in Northern Sweden from a population of 250 000	25–85
France	65.8	632.8	500	200	22–86
Italy	60.8	302.1	500–600	250	25–85
Spain/Majorca ^a	46.5	506.0	27	58	40–75
Bulgaria	7.3	110.0	41	14	44–63
Germany	80.5	357.3	120	60	28–69
Netherlands	16.8	41.5	45	23	25–75
Cyprus ^a	0.9	9.3	50	140	20–75
Turkey	75.0 ^b	783.6 ^b	20–30	16	21–66

TTR, transthyretin; TTR-FAP, transthyretin familial amyloid polyneuropathy. Information compiled from clinical experience of the European Network for TTR-FAP (ATTReuNET) in March 2014, unless otherwise referenced.

^aTends to be early-onset.

^bInformation from alternative source [37].

accounts for 50% of TTR-FAP mutations worldwide [30^{***}]. Within Europe, the mutation is believed to have arisen independently in Portugal and Sweden [4,43] (where it is responsible for most, but not all, cases), as well as Italy [44]. Furthermore, Val30Met is the only mutation so far identified in endemic regions of Cyprus and Majorca [31,32].

In nonendemic countries, such as France, Italy, and Germany, there is genetic heterogeneity. In France alone, more than 29 mutations of the *TTR* gene have been identified up to 2012; TTR Val30Met mutation is the most common, occurring in 62% of cases [22]. This may relate to a large immigration from Portugal to France in the early 1970s [45]. Point mutations at TTR residue Ser77 (Tyr77 and Phe77) account for the remaining 11.8 and 6.2% of French cases, respectively [22]. Figure 2 shows the geographical localization of TTR genotypes in France, Germany, Italy, Portugal, and Sweden, and Figure 3 uses data gathered from our survey to depict the three most common point mutations observed in each of the participating countries. The most common mutation in Europe, with the exception of Bulgaria, is Val30Met, but there is heterogeneity around the second-most prevalent mutation (Figure 3).

Penetrance

Penetrance refers to the probability that a genetic trait will be expressed in people who carry the gene mutation. If penetrance is less than 100%, or incomplete, carriers of the gene may remain

asymptomatic, yet their children can be affected clinically [4]. The management of asymptomatic carriers of mutated TTR is covered in more detail in the third article in this series [46].

In Piteå and Skellefteå, areas of northern Sweden in which TTR-FAP is endemic, the frequency of the Val30Met mutation is 2% [38]; however, penetrance is relatively low (1.7% at 30 years, 22% at 60 years) and far from complete (69%) by age 90 years [39]. Yet the penetrance is significantly higher with a risk of earlier onset when the mutation is inherited from the mother rather than from the father [39,47^{***}]. Penetrance can also vary geographically, with the Portuguese population showing much higher penetrance of the Val30Met mutation during middle age (80% at 50 years) compared with the French population (18% at 50 years) [48]. The impact of penetrance on age at onset of TTR-FAP and the clinical presentation of the disease have important implications in terms of patient management.

Clinical presentation of transthyretin familial amyloid polyneuropathy

The clinical presentation of TTR-FAP is governed by an interplay between a number of factors, including genotype and geographical origin of the patient, regional variation, penetrance of the gene mutation, and age at onset of symptoms. Consequently, there is a wide spectrum of phenotypes associated with TTR-FAP [2,8,49,50].

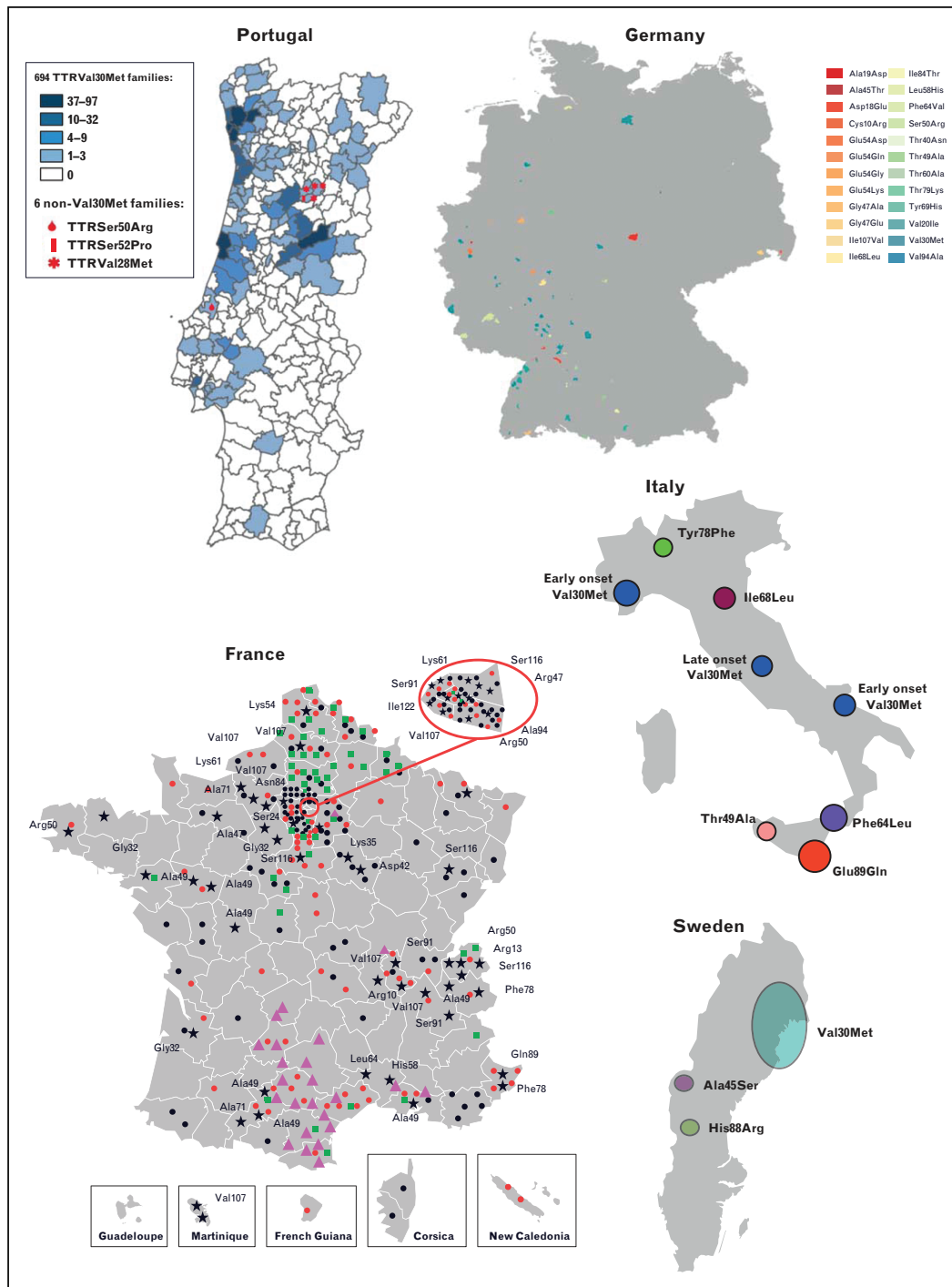


FIGURE 2. Location of TTR genotypes in Portugal, Germany, France, Italy and Sweden. TTR, transthyretin. Portugal: Family distribution according to region of origin. Seven families are from Madeira island (nonrepresented). Courtesy of Teresa Coelho, 2015. Germany: Geographic distribution of patients seen at the Heidelberg Amyloidosis Centre. Courtesy of Ernst Hund, 2014. France: Distribution of FAP in France. TTR Met30 Port (full black circles); TTR Met30 non Port (full red circles); TTR Tyr77 (green full square); TTR Phe77 (pink full triangles); stars: non Met30 TTR-FAP (neither Tyr77, nor Phe77; in details). In red circle, enlargement of Paris and its inner suburbs is depicted. TTR Met30 Port is mainly found in Paris region, TTR Met30 non Port is more ubiquitous. TTR Tyr77 is mainly found in northern France and TTR Phe77 in south western. Other mutations are scattered across the entire territory. Adapted from Adams *et al.* [22]. Italy: Distribution of TTR genotypes across Italy. Courtesy of Laura Obici, 2015. Sweden: Origin and clustering areas of the three most common mutations in Sweden. In the remaining areas of Sweden, there are sporadic cases of predominantly Val30Met, with 11 additional mutations identified. Courtesy of Ole B. Suhr, 2015.

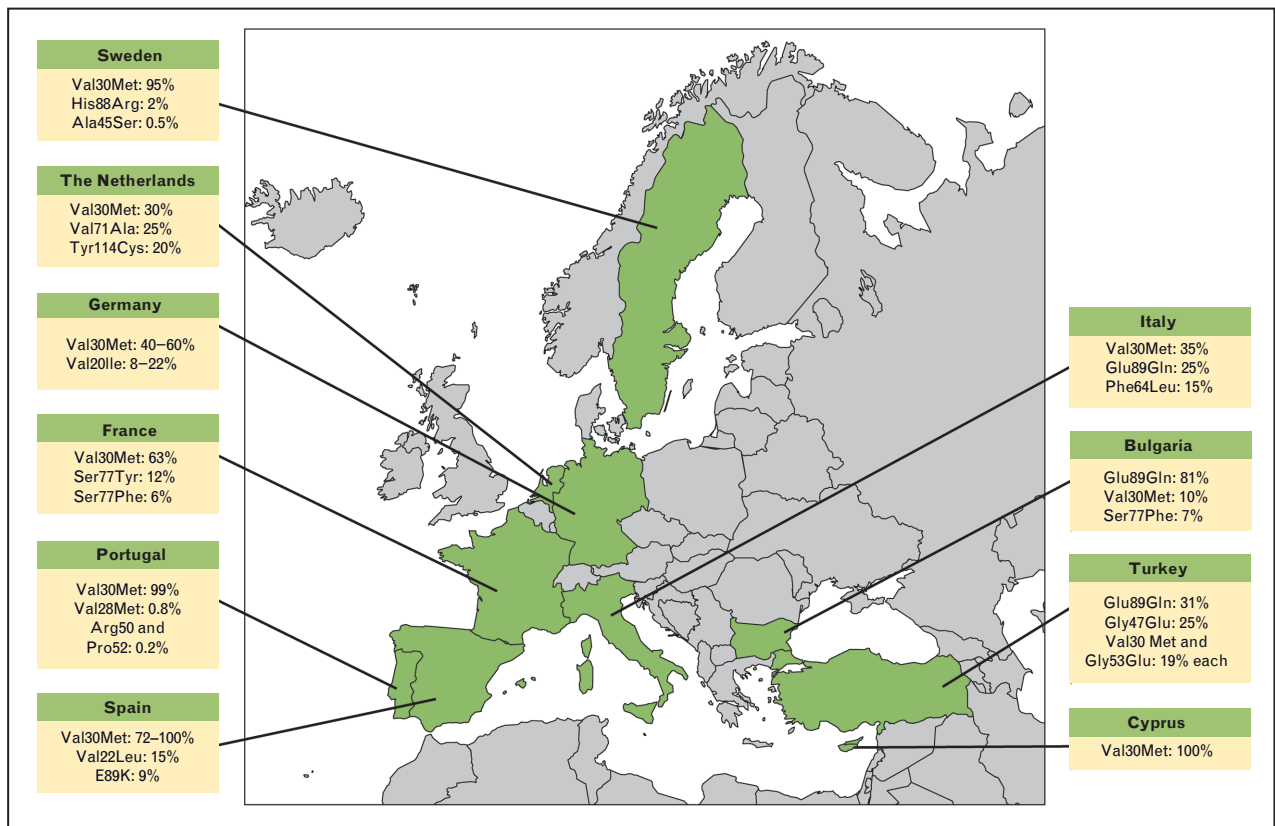


FIGURE 3. The most frequent TTR point mutations observed across Europe. TTR, transthyretin. Data compiled from clinical experience of the European Network for TTR-FAP (ATTReNET) in March 2014.

Age at onset of disease-related symptoms

The phenotype of TTR-FAP is associated with sex and age of onset, whereby male patients with a late onset (age >50 years) have increased risk of developing cardiomyopathy and heart failure [51,52,53]. Figure S1, <http://links.lww.com/CONR/A35> shows how the mean age at onset of TTR-FAP-related symptoms varies among European countries. The average age of onset of disease observed in Portugal is 33.5 years, with 87% of patients developing symptoms before age 40 years ($n = 1233$) [35]. Within the same patient cohort, women were found to have a significantly later onset than men (33.7 vs 29.0 years; $P < 0.001$) [35]. The age at disease onset tends to be later in Sweden (56–57 years) [54,55], a trend mirrored in other countries of nonendemic TTR-FAP, including Germany and Italy [56,57]. In a small cohort from the Netherlands ($n = 7$), age at first symptom appearance ranged from 33 to 69 years [58].

Our survey has shown that in the countries represented by the ATTReNET, the age range of patients with TTR-FAP is broad and varies from the second to the ninth decades of life (Table 1), except Bulgaria and Turkey, which estimate an older and comparatively narrower window (44–63 years and

21–66 years, respectively). Onset of symptoms can be described as bimodal, with one peak in the third to fourth decade of life (early onset) and another distinct peak in the sixth decade of life (late onset) [6].

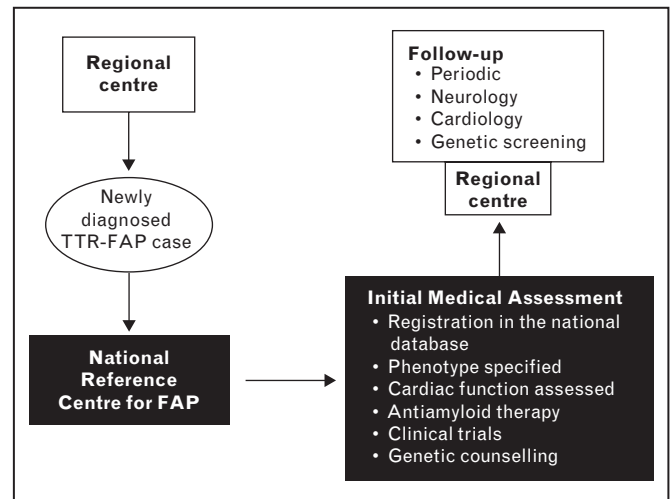


FIGURE 4. The referral process for TTR-FAP patients in France. FAP, familial amyloid polyneuropathy; TTR-FAP, transthyretin familial amyloid polyneuropathy. Information compiled from clinical experience of the European Network for TTR-FAP (ATTReNET) in March 2014.

Clinical features of transthyretin familial amyloid polyneuropathy

Within most of the regions in which it is endemic (Portugal, Cyprus, and Majorca), TTR-FAP often occurs before age 40 years (early onset), with progressive sensory-motor and autonomic neuropathy, leading to cachexia and eventually death within, on average, 10.8 years of disease onset [7,48,59]. Length-dependent small-fibre sensory-motor polyneuropathy with life-threatening autonomic dysfunction is a distinguishing feature of TTR-FAP in these regions, but frequently, there is also cardiac (conduction disturbance), renal, and ocular involvement [60¹¹].

In nonendemic areas, and in endemic regions of Sweden, the onset of disease-related symptoms tends to be later in life, from age 50 years onward [54,55], and a male predominance for the late-onset TTR-FAP has been observed [55,61]. Neuropathy tends to affect all fibres and may closely resemble chronic inflammatory demyelinating polyneuropathy [61,62]. Upper limb onset [63], motor neuropathy [64], and ataxic polyneuropathy [56] are all possible presentations of late-onset disease. Typically, sensory and motor neuropathy symptoms of upper and lower extremities occur, associated with mild autonomic symptoms [61].

The wider variation in genotype among patients with late-onset disease (~40 variants) confers a broader spectrum of clinical features, which continues to evolve the phenotypic profile of the disease. For example, the TTR Gly47Glu mutation has been associated with mild peripheral neuropathy and cardiac involvement [58]. Compared with the TTR Val30Met mutation, TTR Glu89Gln is associated with higher left ventricular mass index, lower left ventricular ejection fraction, shorter E-wave deceleration time, more severe cardiomyopathy, and higher risk of major cardiovascular events [65]. Among TTR Val30Met patients, the occurrence of cardiomyopathy is generally age-related, presenting predominantly in late-onset male patients [51¹¹,52].

The high variability in age at symptom onset may serve to complicate the diagnostic process, but the importance of early diagnosis in TTR-FAP patients cannot be overemphasized, particularly as late-onset TTR-FAP often has a more severe course [60¹¹].

Existing structures and resources

The ATTReuNET panel acknowledge that while the management of patients differs widely across Europe, there are certain similarities in the overall patient experience, or journey. Overall, our findings indicate a clear need for the consolidation and coordination of expertise.

Barriers to optimal management of transthyretin familial amyloid polyneuropathy

One robust theme to emerge from panel discussions was delay in diagnosis, with the majority of patients tending to see between three and four physicians before they receive an accurate diagnosis of TTR-FAP (Table S2, <http://links.lww.com/CONR/A37>). Only representatives from Portugal, Sweden, and Cyprus reported that patients generally consulted fewer than two physicians before diagnosis. Delay in diagnosis is most pronounced in areas where TTR-FAP is not endemic and when there is no positive family history, including in endemic areas [2,2,12]. Questionnaire data show that diagnosis was generally quicker in patients with a positive family history (~2 years), but could be up to 5 years in the general patient cohort (Table S2, <http://links.lww.com/CONR/A37>).

The availability of *TTR* gene testing further facilitates the speed of diagnosis, particularly in endemic regions. However, in areas where there is greater genotypic variation, the diagnostic process can become confused by similarities with other types of neuropathy and incomplete sensitivity of biopsies used to identify amyloid deposits. It may also be the case that biopsy and genetic testing facilities are not widely accessible in all countries. Genetic testing for Val30Met may have limited diagnostic impact and reliability when applied with populations with low-penetrance variants and high gene frequency, such as northern Sweden [38,39].

The ability to recognize phenotypic variations of TTR-FAP is an important skill that requires appropriate training. Questionnaire data presented in Figure S2, <http://links.lww.com/CONR/A36> describe the ambulatory status of patients at diagnosis and show that in most countries, the majority of patients have no mobility difficulties when they first present to the physician.

Even after diagnosis, a lack of standardized treatment strategies may negatively impact patient outcomes. Treatment approaches and the availability of oral therapeutic agents may vary even within regions of the same country. Many funding bodies do not provide financial coverage for diagnosis and management of TTR-FAP while the patient is still able-bodied. The next article in this series presents the expert group consensus on diagnosis, treatment, and management of TTR-FAP [66].

A network approach for transthyretin familial amyloid polyneuropathy

NRCs are a means to ensure equity of access to early and appropriate diagnosis, treatment, and care, and

Table 2. Benefits associated with the network approach

Network approach					
Awareness and education (healthcare professionals and general public)		Facilitation of research		Informed policy decisions	
Increased screening	Earlier diagnosis	Collaboration	Greater uptake of clinical trials	Access to treatment	Approval of new therapies

Information compiled from clinical experience of the European Network for TTR-FAP (ATTReuNET) in March 2014.

to eliminate regional disparities in treatment approaches. Most of the 10 countries involved with the ATTReuNET have at least one defined NRC (Table S3, <http://links.lww.com/CONR/A37>). The establishment of NRCs can encourage collaboration and the sharing of experience between different centres and motivate the teams working within them. A defined network also lends credibility and weight to the disease in proposals to public authorities for disease funding, such as coordinated research programmes. A multifaceted disease such as TTR-FAP lends itself well to this approach and serves to benefit patients. Existing initiatives include clinical guideline recommendations for diagnosis and management [4], as well as an international patient database to gather outcome information for a fuller clinical picture of the disease [67]. Moving forward, the panel recognizes the importance of drawing upon the experiences of similar networks for other rare inherited diseases (e.g. Charcot–Marie–Tooth disease and Duchenne muscular dystrophy).

A network has many benefits, including the potential for an increase in the number of newly diagnosed cases at the national level, and increased satisfaction among specialists in regional centres (e.g. education and independence) and from patients and their families. In addition, patients who are cared for by a multidisciplinary team at their regional centre will benefit from access to the best available recommended therapies.

The French model (the national plan for rare diseases)

The French National Network for TTR-FAP has been pivotal in improving the diagnosis of new cases and raising the quality of care for patients with the disease at the national level. The panel agreed that the system represents a good working example on which to base future initiatives in other countries. The National Plan for Rare Diseases in France was first established in 2004 with 131 NRCs certified by the French Health Ministry to ensure equity of access to diagnosis, treatment, and care; one of them concerned FAP [68,69]. These centres were selected

because of the characteristics of the disease, including severe chronic pain, motor problems, sensory deficit, disturbance of autonomic function, and life-threatening disease.

The mission statements of the national plan included the facilitation of diagnosis and strategy for therapeutic, psychological, and social support; the definition and differentiation of protocols for care; the coordination of research; and the provision of training to healthcare professionals, patients, and their families, to direct and coordinate networks of healthcare professionals (medical and social) [68]. Networked treatment centres are both multicentric and multidisciplinary, bringing together all aspects of patient care; including, for example, neurology, cardiology, liver transplant, nephrology, ophthalmology, physiotherapy, and pain management. The referral process in France, under the network approach, is summarized in Figure 4. As well as fostering collaboration between medical experts and thereby guiding public health policy, the French network also liaises with the Association Française Contre L’Amylose, a TTR-FAP patient support group.

The development of a French network for TTR-FAP was facilitated by the labelling of 10 centres for neuromuscular diseases in the same way as the national plan for rare diseases (2005–2008). These centres are distributed throughout the country and include specialists for rare peripheral neuropathies who are considered as regional referents and correspondents for FAP. The network approach allows for the education of physicians about FAP, to update their knowledge and ensure they have the support of other necessary specialists (e.g. cardiologists and geneticists).

To meet the specifications of the French Health Ministry, the French NRC for FAP (NNERF) organized the first conference for TTR-FAP in 2009, inviting professionals, patients, and families to discuss and debate issues surrounding the disease and management options. In 2010, the NNERF launched a website (<http://www.nnerf.org>), and in 2012, the characteristics of French patients recruited with the help of the network were published [22].

Benefits associated with a European network

The existing network among Italian NRCs has also contributed significantly to improved diagnosis and awareness of TTR-FAP. The initiative has also enabled gathering of information on the natural history of the disease in nonendemic areas and promoted participation in clinical trials. In Spain, a consensus group is currently working to establish common, national guidelines for the care and treatment of TTR-FAP. Sweden is also in the process of developing a national network. Portugal has two multidisciplinary centres, in Lisbon and Porto, that are recognized by patients, families, and healthcare personnel as being the most appropriate places of assistance for these patients. In 2012, the Portuguese Ministry of Health designated them as the only prescribers of oral medication fully reimbursed by the Portuguese National Health System. The development of formally recognized NRCs is now occurring and should be in place before the end of the year. These two centres have been recently formally recognized as the NRCs for FAP in Portugal.

Through the hosting of two national advisory board meetings of neurologists specializing in TTR-FAP, progress has been made in Turkey, a country currently lacking a multidisciplinary approach to treatment. Increased disease awareness and diagnosis of new patients has been a key consequence of these meetings. The use of global patient registries is essential to chart the natural history of rare diseases like TTR-FAP, and to this end, the THAOS (Transthyretin Amyloidosis Outcomes Survey) registry has recently been established [67].

The benefits associated with a network approach to TTR-FAP management are summarized in Table 2. It is anticipated that raising awareness of TTR-FAP, not just among healthcare professionals but among patients and their families as well, will lead to increased rates of screening and improved rates of detection. Earlier diagnosis is the key to the more effective management of patients.

CONCLUSION

TTR-FAP is a rare, yet devastating, systemic disorder with predominant neurologic involvement that persists throughout Europe, with high genotypic variability. Fibre length-dependent sensory-motor and autonomic neuropathy are neurological hallmarks of TTR-FAP, although additional neuropathic, gastrointestinal, cardiovascular, renal, and ocular symptoms all contribute to the phenotypic heterogeneity of the disease. Given these differences, it

follows that patient management strategies lack standardization at the regional, national, and international level. The formation of the ATTreUNET is the first step in an ongoing transformative process seeking to standardize disease management across Europe. A collaborative, fully networked approach to TTR-FAP management will permit the sharing of resources and expertise and will ultimately allow all patients access to the highest standards of clinical care. The immediate 5-year aim is to network existing NRCs from the countries represented in the current panel, with a view to then expanding into other countries through the creation of new NRCs. In 10 years, it is hoped that the network will serve all European countries affected by TTR-FAP. The group may also consider application for EU funding for epidemiological and genetic studies, and to support advocacy group development for empowerment of patients and families.

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Conflicts of interest

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