Recommendations for presymptomatic genetic testing and management of individuals at risk for hereditary transthyretin amyloidosis

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Purpose of review
These recommendations highlight recent experience in genetic counselling for the severe autosomal-dominant, late-onset transthyretin familial amyloid polyneuropathy (TTR-FAP) disease, and present a structured approach towards identification and monitoring of asymptomatic carriers of the mutated gene.

Recent findings
The effectiveness of current treatment options is still limited in patients with TTR-FAP beyond stage I. Diagnosis in the early stages of TTR-FAP is essential to prevent or delay the progression of disease. Existing legal and cultural issues differ among countries within Europe. Experts of the European Network for TTR-FAP (ATTReuNET) concluded that genetic counselling for diagnosed individuals and at-risk family members is mostly beneficial and should be carried out with care by trained professionals. Systematic and regular monitoring of an asymptomatic carrier is necessary to detect early signs of TTR-FAP and maximize the effectiveness of treatment. This includes five areas of assessment: history/clinical examination, sensorimotor function, autonomic dysfunction, cardiac function, and renal function. At least two related symptoms and positive biopsy findings are required to confirm diagnosis of TTR-FAP.

Summary
Early detection of TTR-FAP is essential to improve the prognosis of TTR-FAP. ATTReuNET recommends genetic counselling and routine monitoring for asymptomatic carriers of TTR-FAP.

Keywords
amyloidosis, asymptomatic, genetic counselling, identification, transthyretin familial amyloid polyneuropathy

INTRODUCTION
Familial amyloid polyneuropathy (FAP) is a rare, life-threatening, autosomal-dominant, systemic disease caused by the extracellular deposition of insoluble amyloid fibrils formed by mutated transthyretin (TTR) \cite{1}. To date, more than 100 missense mutations in the TTR gene have been described worldwide; however, not all are amyloidogenic \cite{2,3,4}. Most of these TTR variants are found in single individuals or within a few families, whereas a few are prevalent in well-defined geographic regions \cite{1,5}. Among these, the Val30Met mutation (indicated as Val50Met according to updated Human Genome Variation Society nomenclature) \cite{6} was the first to be identified and is by far the most common \cite{7}.

Transthyretin FAP (TTR-FAP) has an estimated prevalence of one in 100,000 in the USA \cite{8} and Europe \cite{9}. It is considered an endemic disease in...
specific areas of Europe (northern Portugal, Sweden, Cyprus, and Majorca) and in Japan [1,5*,10].

TTR-FAP presents in many different forms and with considerable variation in signs and symptoms among individuals and across geographic locations [5*]. Symptoms are mainly neuropathic, including a heterogeneous presentation of peripheral (sensory and motor) and autonomic neuropathy. In addition, gastrointestinal impairment, cardiomyopathy, nephropathy, or ocular deposition can be associated with neurological disease [5*].

Diagnosis in the early stages of TTR-FAP is essential to allow for timely treatment to prevent or delay disease progression. Early recognition remains a challenge, with delayed diagnosis still occurring, often because of misdiagnosis [11–16]. Time to diagnosis can be as long as 4 years, especially among those without a family history of FAP, because of low penetrance of the gene or the rare occurrence of de novo mutations [11–13,16,17**].

An additional challenge arising once the disease is recognized in a single family member relates to proper genetic counselling and the offer of presymptomatic genetic testing (PST) for the TTR gene to at-risk relatives, followed by effective management of asymptomatic individuals carrying the TTR gene variant [18**]. However, guidelines for early monitoring and diagnosis of asymptomatic carriers of mutated TTR-FAP remain lacking.

In November 2012 and March 2014, two roundtable European Expert Meetings titled ‘Optimising the Management of TTR-FAP in Europe’ were attended by 15 TTR-FAP experts to share expertise and achieve a consensus on the diagnosis and clinical management of TTR-FAP. These experts are members of an emerging group that is provisionally called the European Network for TTR-FAP (ATTReuNET), covering 10 European countries and nine national reference centres.

The questionnaire used in preparation for the meetings (Table S1, http://links.lww.com/CONR/A38) and a summary of the expert participants of ATTReuNET (Table S2, http://links.lww.com/CONR/A38) are provided in the supplementary appendix. In this article, we address the medical, psychological, ethical, and legal aspects of PST among individuals at risk for TTR-FAP, and provide recommendations for following up asymptomatic carriers of TTR-FAP until their first symptoms manifest and they become diagnosed patients. Specific questions related to these issues were addressed by the ATTReuNET group after analysing available published data. Recommendations were developed based on this analysis and face-to-face expert discussions.

Presymptomatic testing for transthyretin familial amyloid polyneuropathy

TTR-FAP is an adult-onset disease, and carriers of the amyloidogenic variant often do not present symptoms until late adulthood [5*]. PST for TTR in at-risk people is now widely available, either at referral centres or at local genetic laboratories [16]. Although accessibility to PST has increased worldwide in the past decade, specific guidelines on the requirements for such testing in TTR-FAP do not exist. As the positive predictive value of PST may vary depending on different populations and mutations, this should also be considered when assessing the risk of developing TTR-FAP for each patient. For example, the prevalence of the Val30-Met TTR mutation in the endemic areas of Sweden is close to 2% [19]; however, the penetrance of the trait varies and is generally low [20], which diminishes the predictive value of PST. In consideration of these aspects and the fact that prophylactic measures are not available for TTR-FAP, the ATTReuNET group discussions focused on whether, how, and when PST should be offered, as well as how to manage the counselling process.

Offer of presymptomatic testing in transthyretin familial amyloid polyn neuropathy

It is generally accepted that the greatest medical benefit from PST can be achieved for diseases for which treatment and/or prophylactic measures are available [21*]. In TTR-FAP, the continuous change in therapeutic options observed in the past 5 years, including medical treatment with tafamidis in the early stage of the disease [22], evidence of possible long-term benefit of liver transplantation in selected cases [23], and novel drugs under clinical development [24], has contributed to changes in the
perception of PST for this disease among physicians and families [25]. PST may allow for close and tailored clinical monitoring until very early signs of the disease arise, prompting treatment initiation, and can help with decisions about personal and family planning, including prenatal and preimplantation diagnosis (PND and PID, respectively) [26*,27].

However, considering the potentially overwhelming impact on personal and family life from a positive test result, a request of PST for TTR-FAP should always originate from the person affected, and communication strategies should be put in place by health professionals to ensure that PST is their autonomous choice [21*]. Limited data collected to date on the psychological impact of PST indicate that it is of potential value in TTR-FAP [25,28**,29]. However, the psychological distress to the patient – in terms of both anxiety and depression, irrespective of a positive or negative result – warrants follow-up and possible long-term psychological support [25]. Interestingly, women are more likely to exhibit long-term anxiety and emotional problems even after a negative result, termed ‘survivor guilt’ [29].

**Timing of presymptomatic testing**

Apart from well-acknowledged general recommendations to avoid PST in minors [30], no guidance is available concerning the best time to offer PST in adults. Considerations about specific genotype–phenotype relationships, age at disease onset, and severity in affected relatives should be taken into account when offering PST [28**]. In particular, the possibility of genetic anticipation, which is the earlier age of onset in subsequent generations of index cases, should be taken into consideration in endemic regions, with higher likelihood of anticipation and earlier age of onset in male offspring inheriting the disease from the mother [31,32,33*]. Early and late-onset disease variants can coexist in the same family, and an understanding of anticipation should be considered when counselling offspring and following up mutation carriers [33*]. Paneque, et al. [28**] showed that prolonged awareness of TTR-FAP in the family and longer personal experience of the disease might contribute to a better adaptation to the knowledge of personal genetic status, as well as reducing the psychological burden of the results. On the contrary, individuals who become aware of the disease in their family only recently before deciding to undergo PST have more difficulties coping with the results [28**].

**Genetic counselling for presymptomatic testing**

Genetic counselling in the context of PST for late-onset diseases presents a series of ethical, psychological, and practical questions. This includes the advantages and disadvantages of knowing a diagnosis well in advance of the appearance of symptoms, the difficulty of living with the results, and the potential impact of this information on reproduction, professional life, and family relationships [18**,21*,34]. In common with other late-onset neurodegenerative diseases and familial cancer syndromes, genetic counselling is of utmost importance when offering PST for a disabling disease like TTR-FAP. Although no specific protocols have been implemented for TTR-FAP, guidelines applicable to several different adult-onset monogenic conditions have been proposed, covering different aspects of the counselling process [21*,35,36]. These guidelines are mainly intended to share the principles and objectives of PST, limiting specific indications (i.e. the number and timing of sessions) to enable practitioners to individualize the protocol according to their judgement and expertise. However, the quality and the content of the information provided in the counselling process, the setting in which communication takes place, the skills of health professionals involved in the service and their capacity to support the psychological impact of the results should be taken into consideration when providing PST [21*].

Several studies have evaluated how counselling can be optimized to provide the best outcome, including consideration of the number of counselling sessions, time spent, consultation environment, multidisciplinary approach, topics for pretest discussion, and follow-up sessions [18**,21*,34]. A recent study of individuals at risk for TTR-FAP indicated that positive perception of PST by consultants also relates to the adjustment of the counselling protocol on a ‘case-by-case’ basis, reflecting counsellor flexibility, experience, self-confidence, and training in establishing empathic relationships [18**].

**Prenatal and preimplantation diagnosis**

Overall, there is limited experience with PND and PID in TTR-FAP in Europe, and most has been gathered in Portugal and, recently, France. For example, in Portugal, both PND and PID are currently available, with a strong recommendation from the National Council for Medically Assisted Procreation (Conselho Nacional de Procriação Medicamente Assistida) for existing patients to undertake PID [37,38]. A survey conducted among FAP carriers between 18 and 35 years found that the choice for controlled reproduction is related to their knowledge about the disease and current socioeconomic position, emphasizing the need to educate families about TTR-FAP [27]. Differences in legal and cultural issues on preimplantation and/or termination of pregnancy between countries within Europe remain
diverse [39]; therefore, providing general recommendations for this setting is a challenge.

**Expert recommendations for genetic counselling and presymptomatic testing**

Based on available literature and the long-term experience gathered at the European centres represented by the expert group, ATTReuNET agreed that PST may be carried out safely in TTR-FAP. This recommendation is based on the emerging benefits of detecting asymptomatic carriers, given the growing availability of medical treatment for this disease and the need to avoid misdiagnosis. However, PST testing should always remain a personal choice, and long-term medical monitoring can be offered as an alternative to those individuals who decide not to undertake PST. The approach and methodology shown in Table 1 and Figure 1, respectively, are recommended for genetic counselling for PST in TTR-FAP.

Because of different rules and regulations among European countries [35,39], no specific recommendation can be provided to healthcare professionals about who should be involved in genetic counselling for TTR-FAP. Genetic counsellors, physicians with expertise in TTR-FAP, and psychologists/psychiatrists should work together as a team whenever possible to provide a multidisciplinary environment that facilitates a sustainable, long-term relationship with patients and at-risk family members (Table 2). A team approach that includes a clinical expert in TTR-FAP will likely improve the amount and quality of the information provided, whereas fostering, from the very beginning, an empathetic relationship with a key person who will be responsible for the index case, should the test result be positive [34]. Genetic counsellors and psychologists can improve the communication process within the team, increase staff skills and experience, and help clinicians to deal with any ambivalent feelings and personal fears [34].

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**Table 1.** ATTReuNET-recommended approach to genetic counselling of asymptomatic carriers

| Genetic counselling should only be employed for those aged ≥18 years |
|---------------------------------------------------------------------|
| PST should be at the request of the patient                           |
| There should be a multidisciplinary approach to genetic counselling, and it should be clear how each team member should be involved |
| Timing of genetic counselling should be determined according to whether the region is characterized by early or late-onset, sporadic, or endemic cases |
| PST requests outside of genetic counselling should not be permitted, unless allowed according to national guidelines and regulations |
| There should be ongoing communication after PST, and the information provided should be updated and current |

**Table 2.** ATTReuNET-recommended methodology in genetic counselling and testing

| Before PST | During PST | Post results |
|------------|------------|--------------|
| • Receive patient request for PST and schedule first appointment  |
| • Signed informed consent* |
| • One or more pretest counselling session according to local practice and regulations |
| • PST performed by a multidisciplinary team, including medical geneticist, TTR-FAP expert, psychologist/psychiatrist |
| • Contact with the psychologist/psychiatrist may occur during all PST processes or be limited to difficult situations only, such as young patients or patients with existing psychiatric problems, or according to local protocols and geneticist/clinical judgement and experience |
| • The TTR-FAP expert maintains contact with the carrier after disclosure of results |
| • The results of genetic testing are disclosed at a face-to-face meeting |
| • Follow-up offered, including direct contact with the psychiatrist in critical cases or on request |
| • A letter is sent home with a summary of discussed items |
| • Neurological and cardiac evaluations to be scheduled according to patient’s wish, taking into account patient’s age and type of mutation |

**FIGURE 1.** ATTReuNET-recommended methodology in genetic counselling and testing. ATTReuNET, European Network for TTR-FAP; PST, presymptomatic testing; TTR-FAP, transthyretin familial amyloid polyneuropathy. *Requirement depending on local regulations.
Although two pretest sessions are generally recommended in published protocols, the number and timing of sessions can vary according to counsellor/team judgement [21,35]. Overall, PST in at-risk relatives may be postponed from the time of diagnosis of the index case, particularly if the disease is an unexpected finding because of a lack of family history. During this period, the priority usually remains with the index case, with the goal being to limit the psychological impact of the new diagnosis on the whole family and allow time to establish a long-term relationship between patient, family, and clinician before wider counselling is implemented.

However, siblings of diagnosed patients/index cases may have a higher priority for genetic counselling, especially for those close to the age of potential disease onset, because they are at the greatest risk for developing symptomatic disease in the short term and could even present with mild signs of disease at first evaluation after a positive test [40]. In contrast, offspring of diagnosed patients/index cases must be approached with sensitivity because of the high likelihood of emotional reactions (e.g. blame, anger, fear) based on knowledge of inheriting a serious disease that cannot be prevented and has limited treatment options available [28]. Time is essential for the family to adjust to diagnosis and
make subsequent decisions (e.g. impact on reproduction, financial matters, career planning) [21*].

**Management of asymptomatic carriers**

Baseline assessment and subsequent regular monitoring of an asymptomatic carrier may be effective in detecting changes in the very initial stages of the disease, given that early diagnosis and prompt treatment currently provide the best chance of minimizing further nerve degeneration [41]. In fact, available treatments appear to be most effective in patients with stage I TTR-FAP [1,5*,42], whereas data supporting efficacy in more advanced stages are limited [43,44]. An effective treatment could delay disease progression, but recovery from established neurological deficits would not be expected. Several studies have been performed to identify neurophysiological markers of early small fibre damage and signs of very initial nerve injury [45,46,47**]. Laser-evoked potentials, sympathetic skin responses, cold and warm detection thresholds and heart rate variability, as indicators of small fibre functioning, have all proven greater sensitivity at detecting early signs of TTR-FAP than conventional neurophysiological large fibre tests [45,46]. In addition, assessment of sudomotor function by means of Quantitative Sudomotor Axon Reflex Test or SUDOSCAN (Impeto Medical, San Diego, CA) may help to disclose early abnormalities of distal small nerve fibre function. There is also evidence to suggest that high-resolution magnetic resonance neurography may detect and quantify peripheral nerve injury in the lower limbs even before TTR-FAP becomes symptomatic in carriers [47**].

It is anticipated that additional understanding of the TTR-FAP disease will be provided by the international collaborative prospective THAOS (TTR Amyloidosis Outcomes Survey) registry [48,49*]. However, to date, no consensus guidelines are available for monitoring asymptomatic TTR carriers, and different protocols have been locally implemented according to everyday practice. These protocols reflect centre-based experiences that are closely related to the spectrum of mutations and phenotypic characteristics of the disease in each region. For example, in populations in which a mixed neurological-cardiac phenotype is mostly observed because of a wide spectrum of TTR variants (e.g. France, Italy), cardiac evaluations may be included very early in carriers at follow-up [26*]. In the Portuguese population, TTR-FAP frequently causes early conduction abnormalities in the absence of echocardiographic signs of cardiomyopathy at onset and may also damage the kidneys in the initial disease stages. Therefore, assessment of cardiac parameters, particularly ECG and 24-hour Holter monitoring, and urine examination are routinely recommended [50,51]. Individuals belonging to families with early-onset TTR-FAP consistently undergo more frequent neurological investigations. Finally, the age at first evaluation relative to the expected age of onset according to genotype may impact on the particular set of examinations performed [33*].

**Expert recommendations for management of asymptomatic carriers**

Methodologically, ATTReuNET identified five areas of assessment – namely, history/clinical examination, sensorimotor function, autonomic dysfunction, cardiac evaluation, and renal function – and agreed on the minimum set of evaluations that should be performed at the time of the first visit after a positive PST (Table 2). To avoid emotional distress, it is recommended that invasive tests are avoided and that the number of evaluations performed each year is limited. The purpose of the follow-up is to provide the earliest identification of disease onset to allow prompt initiation of treatment. Educating presymptomatic carriers to recognize the early disease-related symptoms is of paramount importance. Assessments that have limited sensitivity and specificity and are not yet able to guide treatment decision-making should be avoided or performed only in the context of a clinical observational research study.

It is recommended that the frequency of follow-up should vary according to the patient’s age, age of onset in the family, and sex of the parent who carries the mutated gene [33*,52*] (Table 2), with the anticipation effect through maternal transmission also taken into consideration [53]. Monitoring could become more frequent when the typical age of onset for that particular mutation/family history is reached. Abnormal findings can prompt a shorter follow-up to clarify their clinical significance. Overall, routine follow-up is recommended yearly in countries with early-onset Val30Met TTR-FAP, such as Portugal, as well as for individuals with late-onset disease. The recommended age to start these evaluations will probably be the major difference between the two types of population.

Biopsies are not routinely recommended for long-term monitoring of asymptomatic carriers because of their invasiveness. In addition, a positive biopsy in the absence of any functional abnormality has no predictive value on the onset of the disease [5*]. The presence of TTR-FAP symptoms is required to initiate treatment even in early-onset Met30 Portuguese carriers with evidence of amyloid deposits from a biopsy [41]. However, biopsy can become helpful to clarify unexpected abnormal findings. On
the other hand, the low sensitivity of biopsies in early stages and/or false-negative results should always be considered before dismissing a clinical suspicion of symptomatic disease [1,5,42,54].

There are insufficient data available to allow for an absolute definition of what represents the minimal evidence of neurological involvement to prompt treatment. Despite the lack of guidance, it is important to be cautious when classifying a carrier as affected, because a diagnosis will determine initiation of treatment. Therefore, more than one abnormal finding should be obtained before a diagnosis can be established. The ATTReuNET members recommended that the key diagnostic indicators for TTR-FAP be at least two of the following TTR-FAP-related symptoms, followed by a biopsy: patient-perceived symptoms or changes, changes from baseline measurements, or cardiac indicator (cardiac microvoltage, pseudomyocardial infarction, or heart blocks).

CONCLUSION

TTR-FAP is a rare but ubiquitous and life-threatening genetic disease. Early diagnosis and intervention is critical, given the still-limited time window for effectiveness of treatment, including liver transplant and pharmacotherapy. PST is an important tool for early patient diagnosis, particularly within those areas in which TTR-FAP is endemic, and will feature strongly in diagnostic protocols of the future. Genetic counselling and PST should be approached with care and carried out by a multidisciplinary team. Overall, there is agreement across Europe that proper genetic counselling in TTR-FAP has beneficial effects, with no significant disadvantages. Raising awareness, establishing TTR-FAP expert networks, and having referral channels to the TTR-FAP NRCs will help to ensure timely detection of the disease and effective delivery of optimal care to patients.

From an ethical perspective, the provision of genetic counselling to individuals with a diagnosis of TTR-FAP is mandatory to provide knowledge of the disease; however, PST should be performed only upon informed patient request. A good long-term relationship between physician, patient, and family may improve adherence to follow-up requirements in asymptomatic individuals after a positive presymptomatic test.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of outstanding interest
• of special interest

1. Adams D, Theaunin M, Cauquil C, et al. FAP neuropathy and emerging treatments. Curr Neurol Neurosci Rep 2014; 14:435.
2. Conners LH, Lim A, Prokavea T, et al. Tabulation of human transthyretin (TTR) variants. Amyloid 2003; 10:160–184.
3. Saura MI. Transthyretin mutations in hyperthyroxinemia and amyloid diseases. Hum Mutat 2001; 17:493–503.
4. Rowczon DM, Noor I, Gilmore JD, et al. Online registry for mutations in hereditary amyloidosis including nomenclature recommendations. Hum Mutat 2014; 35:E2403–E2412.
5. A valuable website to verify variant classification and genotype–phenotype relationship in TTR-FAP and other hereditary amyloidoses.
6. Rowczon DM, Noor I, Gilmore JD, et al. Online registry for mutations in hereditary amyloidosis including nomenclature recommendations. Hum Mutat 2014; 35:E2403–E2412.
7. Ueda M, Ando Y. Recent advances in transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis 2013; 8:31.
8. A comprehensive study highlighting diagnostic approaches and assessment tools in TTR-FAP.
9. Rowczon DM, Noor I, Gilmore JD, et al. Online registry for mutations in hereditary amyloidosis including nomenclature recommendations. Hum Mutat 2014; 35:E2403–E2412.
10. Bensen M. Amyloidosis. In: Scriv CR, Beaudet AL, Vellde D, et al., editors. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill; 2000 pp. 5345–5378.
11. Examples of prevalence sources previously considered in orphan medicinal product designation procedures. European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500179298.pdf. [Accessed 26 November 2015]
12. Reines JB, Vera TR, Martin-MU, et al. Epidemiology of transthyretin-associated familial amyloid polyneuropathy in the Majorcan area: Son Llatzer Hospital descriptive study. Orphanet J Rare Dis 2014; 9:29.
13. Cappellani M, Cavallo T, Ferrarini M, et al. Variable presentations of the transthyretin-related familial amyloid polyneuropathy in seventeen patients. J Peripher Nerv Syst 2011; 16:119–129.
14. Koike H, Hashimoto R, Tomita M, et al. Diagnosis of sporadic transthyretin Val30Met familial amyloid polyneuropathy: a practical analysis. Amyloid 2011; 18:53–62.
15. Plante-Bordeneuve V, Ferreira A, Laki T, et al. Diagnostic pitfalls in sporadic transthyretin familial amyloid polyneuropathy (TTR-FAP). Neurology 2007; 69:693–698.
16. Dohrn MF, Rocken C, De Bleeker FL, et al. Diagnostic hallmarks and pitfalls in late in life progressive transthyretin-related amyloidosis. J Neurol 2016; 263:3093–3108.
17. Adams D, Lozeron P, Theaunin M, et al. Regional difference and similarity of familial amyloid polyneuropathy with phenace. Amyloid 2012; 19:61–84.
18. Parman Y, Adams D, Obici L, et al. 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. Curr Opin Neurol 2015. (In press).
19. Plante-Bordeneuve V, Said G. Familial amyloid polyneuropathy. Lancet Neurol 2011; 10:1086–1097.
20. An interesting review of pathological, clinical, and neuropathological changes associated with TTR-FAP.
21. Guimarães L, Sequeiros J, Skirton H, Pannee M. What counts as effective genetic counselling for presymptomatic testing in late-onset disorders? A study of the consultant’s perspective. J Genet Couns 2013; 22:437–447.
22. A valuable contribution to the development of an effective counselling process for presymptomatic testing in TTR-FAP.
23. Olsson M, Jonason J, Cedergren K, Suhr OB. Frequency of the transthyretin val30met mutation in the northern Swedish population. Amyloid 2002; 9:124–133.
24. Hellman U, Alarcon F, Lundgren HE, et al. Heterogeneity of penetrance in familial amyloid polyneuropathy, ATTR Val30Met, in the Swedish population. Amyloid 2009; 15:181–186.
25. Skirton H, Lemos C, Alves-Ferreira M, et al. Overcoming artefact: anticipation in 284 Portuguese kindreds with familial amyloid polyneuropathy (FAP) ATTRVM30. J Neurol Neurosurg Psychiatry 2014; 85:326–330.
26. The study finally confirms genetic anticipation as a true biological phenomenon in TTR-FAP.
27. Paneque M, Mendes A, Guimaraes L, et al. Genetics health professionals’ views on quality of genetic counseling service provision for presymptomatic testing in late-onset neurological diseases in Portugal: core components, specific challenges and the need for assessment tools. J Genet Couns 2014; 23:616–625.
28. Goldman JS, Hahn SE, Catania JW, et al. FAP screening: a systematic review of guidelines and position papers. Curr Opin Neurol 2015. (In press).
29. An interesting study that highlights variables affecting the psychological outcome of presymptomatic genetic testing in TTR-FAP.
30. Graceffa A, Russo M, Vita GL, et al. Psychosocial impact of presymptomatic genetic testing for transthyretin amyloidic polyneuropathy. Neuromusc Disord 2009; 19:44–48.
31. Borry P, Stuthens L, Nys H, et al. Presymptomatic and predictive genetic testing in minors: a systematic review of guidelines and position papers. Curr Genet 2006; 70:374–381.
32. Yamamoto K, Ikeda S, Hanu Y, et al. A pedigree analysis with minimised ascertainment bias shows anticipation in Met30-transthyretin related familial amyloid polyneuropathy. J Med Genet 1998; 35:23–30.
33. Duggie U, Anderson R, Chizzari F, et al. Familial amyloid polyneuropathy in Sweden: a pedigree analysis. J Med Genet 1993; 30:388–392.
34. Lemos C, Coelho T, Alves-Ferreira M, et al. Oncoming artefact: anticipation in 284 Portuguese kindreds with familial amyloid polyneuropathy (FAP) ATTRVM30. J Neurol Neurosurg Psychiatry 2014; 85:326–330.
35. A valuable contribution to the development of an effective counselling process for presymptomatic testing in TTR-FAP.
36. The study finally confirms genetic anticipation as a true biological phenomenon in TTR-FAP.
37. Panneque M, Mendes A, Guimaraes L, et al. Genetics health professionals’ views on quality of genetic counseling service provision for presymptomatic testing in late-onset neurological diseases in Portugal: core components, specific challenges and the need for assessment tools. J Genet Couns 2014; 23:616–625.
38. Goldman JS, Hahn SE, Catania JW, et al. FAP screening: a systematic review of guidelines and position papers. Curr Opin Neurol 2015. (In press).
39. MacLeod R, Tibben A, Frontali M, et al. Recommendations for the predictive genetic test in Huntington’s disease. Clin Genet 2013; 83:221–231.
40. Almeida VM, Costa PM, Moreira P, et al. Birth of two healthy females after preimplantation genetic diagnosis for familial amyloid polyneuropathy. Reprod Biomed Online 2005; 10:641–644.
41. Valdrè K, Alves E, Coelho T, et al. [Prevalence of use of preimplantation genetic diagnosis in Unidade Clinica de Paraïmido from Centro Hosi tular do Porto, Acta Med Port 2014; 27:710–718.
42. Steering Committee on Bioethics (CDBI) Secretariat. Background document on preimplantation and prenatal genetic testing. Council of Europe, 2010.
43. A valuable contribution to the development of an effective counselling process for presymptomatic testing in TTR-FAP.
44. Seikjima Y, Yoshida K, Tokuda T, Ikeda S. Familial transthyretin amyloidosis. GeneReviews 2015; http://www.ncbi.nlm.nih.gov/books/NBK1194/ [Accessed 2 June 2015]
45. Adams D, Suhr OB, Eust D, et al. First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. Curr Opin Neurol 2015. (In press).
46. Hallouh RA, Lavrovskaya E, Mody DR, et al. Diagnosis and typing of systemic amyloidosis: the role of abdominal fat pad fine needle aspiration biopsy. Cytojournal 2010; 7:24.
47. Erizcon B, Wilczek HE, Larsson M, et al. Liver transplantation for hereditary transthyretin amyloidosis: after 20 years still the best therapeutic alternative? Transplantation 2015; 99:1847–1854.
48. Hausser RP, Kay MA. RNA interference. Drugging RNAi. Science 2015; 347:1069–1070.
49. Role of the disease in the psychological impact of pre-symptomatic testing for SCA2 and FAP ATTRVM30: experience with the disease, kinship and gender of the transmitting parent. J Genet Couns 2009; 18:483–493.
50. Adams D, Cauquil C, Theaurin M, et al. Current and future treatment of amyloidopathies. Expert Rev Neurother 2014; 14:1437–1451.
51. A valuable contribution to the development of an effective counselling process for presymptomatic testing in TTR-FAP.
52. An interesting study that highlights variables affecting the psychological outcome of presymptomatic genetic testing in TTR-FAP.
47. Kollmer J, Hund E, Hornung B, et al. In vivo detection of nerve injury in familial amyloid polyneuropathy by magnetic resonance neurography. Brain 2015; 138:549–562.

An innovative approach to the detection of early signs of nerve damage in TTR-FAP that might impact on the management of mutation carriers.

48. Plante-Bordeneuve V, Suhr OB, Maurer MS, et al. The Transthyretin Amyloidosis Outcomes Survey (THAOS) registry: design and methodology. Curr Med Res Opin 2013; 29:77–84.

49. Coelho T, Maurer MS, Suhr OB. THAOS-The Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. Curr Med Res Opin 2013; 29:63–76.

The first analysis of a large, longitudinal group analysis in patients with hereditary and wild-type TTR amyloidosis evidenced phenotypic heterogeneity which is multisystemic and emphasized the need for multidisciplinary care.

50. Lobato L, Beirao I, Silva M, et al. Familial ATTR amyloidosis: microalbuminuria as a predictor of symptomatic disease and clinical nephropathy. Nephrol Dial Transplant 2003; 18:532–538.

51. Lobato L, Roche A. Transthyretin amyloidosis and the kidney. Clin J Am Soc Nephrol 2012; 7:1337–1346.

52. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis 2013; 8:31.

A comprehensive paper highlighting diagnostic approaches and assessment tools in TTR-FAP.

53. Bonati B, Olsson M, Hellman U, et al. TTR familial amyloid polyneuropathy: does a mitochondrial polymorphism entirely explain the parent-of-origin difference in penetrance? Eur J Hum Genet 2010; 18:948–952.

54. Daoko J, Elnahar Y, El Kersh K. Cardiac MRI detection of a rare case of familial cardiac amyloidosis (Ser23Asn): case report with literature review. Rep Med Imaging 2010; 3:123–127.