# Familial Portuguese Polyneurotic Amyloidosis

Authored by

**mohammad looti**

September 28, 2025

# Familial Portuguese Polyneurotic Amyloidosis

**Primary Disciplinary Field(s): Medicine**, **Neurology**, **Genetics**, **Cardiology**

## 1. Core Definition

Familial Portuguese Polyneurotic Amyloidosis (FAP), also widely known as transthyretin amyloidosis (ATTR amyloidosis) or hereditary transthyretin amyloidosis (hATTR amyloidosis), represents a rare, progressive, and often fatal genetic disorder. This condition is characterized by the systemic accumulation of abnormal protein deposits, known as amyloid fibrils, primarily within the peripheral and autonomic nervous systems, but also significantly impacting the heart, kidneys, and gastrointestinal tract. The disease typically manifests in adulthood, with the onset of symptoms ranging from the second to the seventh decade of life, and its progression leads to severe multi-organ dysfunction and a significant reduction in life expectancy if left untreated.

The nomenclature for this complex disease is extensive, reflecting its multifaceted nature and historical discovery. Beyond its primary designation, it is recognized by numerous aliases, including transthyretin-related hereditary amyloidosis, Corino de Andrade's disease (named after the physician who first extensively described it), Portuguese polyneuritic amyloidosis, familial amyloid polyneuropathy, Swiss type amyloid polyneuropathy, and Transthyretin familial amyloid polyneuropathy. These various names underscore the diverse clinical presentations and the genetic and geographic specificities associated with different forms of the condition.

At its pathological core, FAP involves the misfolding and aggregation of the transthyretin (TTR) protein. Normally, TTR functions as a transport protein for thyroxine and retinol (Vitamin A) in the blood and cerebrospinal fluid. However, due to specific genetic mutations, the TTR protein becomes unstable, dissociates into monomers, and misfolds, subsequently aggregating into insoluble amyloid fibrils. These fibrils deposit extracellularly in various tissues and organs, leading to progressive cellular damage and organ dysfunction, ultimately compromising the physiological integrity and function of the affected systems.

## 2. Etymology and Historical Development

The designation "Portuguese" in the disease's name is not arbitrary; it signifies the historically high prevalence and initial comprehensive description of this specific form of amyloidosis within certain regions of Portugal. This geographical concentration pointed towards a genetic basis rooted in a founder effect, where a specific TTR gene mutation originated in a small population and subsequently spread through generations. The particular mutation most commonly associated with the Portuguese variant is the Val30Met (p.Val50Met) mutation, which accounts for a substantial proportion of global hATTR amyloidosis cases.

The pioneering work of Dr. Corino de Andrade in the mid-20th century was instrumental in establishing Familial Portuguese Polyneurotic Amyloidosis as a distinct clinical entity. Working in Portugal, he meticulously documented the clinical syndrome affecting numerous families, characterized by progressive peripheral neuropathy, autonomic dysfunction, and other systemic manifestations. His detailed observations and epidemiological studies provided the foundational understanding of the disease, leading to its recognition as a significant inherited disorder and laying the groundwork for future genetic and biochemical investigations.

Following de Andrade's initial descriptions, scientific understanding of FAP evolved from purely clinical observations to a sophisticated biochemical and genetic comprehension. The identification of amyloid deposits as the pathological hallmark, followed by the characterization of the TTR protein as the precursor to these deposits, marked significant milestones. The subsequent pinpointing of specific mutations in the *TTR* gene solidified the genetic basis of the disease, transforming it from a mysterious familial affliction into a genetically defined, inherited protein misfolding disorder. This progression in understanding has been crucial for developing targeted diagnostic tools and, more recently, disease-modifying therapies.

## 3. Genetic Basis and Pathophysiology

The genetic cornerstone of Familial Portuguese Polyneurotic Amyloidosis lies in specific mutations within the *TTR* gene, located on chromosome 18. This gene provides instructions for the synthesis of the transthyretin protein, which normally circulates as a tetramer (a structure composed of four identical protein subunits). The TTR protein plays a vital role in the transport of the thyroid hormone thyroxine and, in complex with retinol-binding protein, transports retinol (vitamin A) throughout the body. There are over 130 known mutations in the *TTR* gene, each potentially leading to varying clinical manifestations and disease progression rates. The Val30Met (p.Val50Met) mutation is the most common worldwide, particularly prevalent in Portugal, Japan, and Sweden, but other mutations can also cause severe disease.

The presence of a mutation in the *TTR* gene leads to the production of an unstable variant of the transthyretin protein. This mutant TTR protein is prone to misfolding; instead of maintaining its stable tetrameric structure, it dissociates into monomers that then undergo conformational changes. These unstable monomers misassemble and aggregate into insoluble amyloid fibrils, which are then deposited extracellularly in various tissues and organs. This pathological process, known as amyloidogenesis, disrupts normal tissue architecture and cellular function, leading to the clinical symptoms observed in FAP. The continuous deposition of these toxic fibrils overwhelms the body's clearance mechanisms, leading to progressive organ damage.

Familial Portuguese Polyneurotic Amyloidosis is inherited in an autosomal dominant pattern, meaning that an individual needs to inherit only one copy of the mutated *TTR* gene from either

parent to be at risk of developing the disease. Despite this, the condition exhibits variable penetrance and expressivity. Variable penetrance refers to the phenomenon where not everyone who inherits the mutated gene will develop symptoms during their lifetime. Variable expressivity means that even among individuals who do develop the disease, the age of onset, severity of symptoms, and rate of progression can differ significantly, even within the same family. These variations are thought to be influenced by other genetic factors, environmental triggers, and lifestyle choices, making the prediction of individual disease trajectories challenging.

## 4. Clinical Manifestations and Progression

The clinical presentation of Familial Portuguese Polyneurotic Amyloidosis is highly heterogeneous, with initial symptoms often involving the peripheral and autonomic nervous systems. Patients commonly experience a progressive sensorimotor polyneuropathy, characterized by tingling, numbness, and burning pain, typically starting in the lower extremities. This can advance to muscle weakness, gait disturbances, and loss of sensation, including temperature discrimination. Autonomic neuropathy manifests as significant gastrointestinal dysfunction (e.g., intractable diarrhea alternating with constipation, early satiety, malabsorption), orthostatic hypotension (a drop in blood pressure upon standing, leading to dizziness or fainting), bladder dysfunction, and erectile dysfunction in males. Carpal tunnel syndrome is also a frequent early symptom, often preceding other neurological manifestations by several years due to amyloid deposition in the wrist ligaments.

Cardiac involvement represents a critical and often life-threatening aspect of FAP. Amyloid fibril deposition in the heart muscle leads to restrictive cardiomyopathy, characterized by increased myocardial wall thickness and stiffness, impairing the heart's ability to fill with blood. This can result in progressive heart failure, characterized by symptoms such as shortness of breath, fatigue, and fluid retention. Furthermore, amyloid infiltration can affect the heart's electrical conduction system, leading to various arrhythmias (e.g., atrial fibrillation) and conduction blocks, which may necessitate pacemaker implantation or increase the risk of sudden cardiac death. The combination of neurological and cardiac manifestations often dictates the overall prognosis and quality of life for affected individuals.

Beyond the neurological and cardiac systems, FAP can affect virtually any organ, contributing to its systemic nature and diverse symptom profile. Renal involvement can lead to proteinuria and progressive kidney disease. Ocular manifestations include vitreous opacities, glaucoma, and dry eyes. Other common symptoms include unexplained weight loss, chronic fatigue, enlarged tongue (macroglossia), easy bruising, and liver damage. Hearing loss, often sensorineural, is also a reported symptom. The insidious onset of symptoms in adulthood, coupled with their non-specific nature, can often lead to significant diagnostic delays, highlighting the importance of considering FAP in patients with unexplained multi-systemic disease, especially those with relevant ancestral backgrounds.

## 5. Diagnosis and Management

The diagnosis of Familial Portuguese Polyneurotic Amyloidosis requires a high index of suspicion, particularly given its varied presentation. The diagnostic process typically begins with a thorough clinical evaluation, assessing symptoms suggestive of polyneuropathy, autonomic dysfunction, and cardiac or renal involvement. Genetic testing for *TTR* gene mutations is paramount for confirming the diagnosis, especially in individuals with a family history of the disease or those from high-prevalence regions. Tissue biopsies (e.g., from the abdominal fat pad, nerve, rectum, or affected organs like the heart or kidney) are often performed to histologically identify amyloid deposits using Congo red staining, which shows characteristic apple-green birefringence under polarized light. Advanced imaging techniques, such as echocardiography, cardiac magnetic resonance imaging (MRI), and technetium-pyrophosphate (Tc-PYP) scintigraphy, are crucial for evaluating cardiac amyloidosis, a key prognostic indicator.

In recent years, significant advancements have been made in the management of FAP, transitioning from purely supportive care to targeted disease-modifying therapies. These therapies aim to halt or slow the progression of amyloid deposition. One class of treatments involves TTR stabilizers, such as tafamidis and diflunisal, which bind to the TTR protein and prevent its dissociation into amyloidogenic monomers. Another revolutionary class comprises gene silencing agents, including small interfering RNAs (siRNAs) like patisiran and antisense oligonucleotides (ASOs) like inotersen. These therapies work by reducing the production of both normal and mutant TTR protein in the liver, thereby decreasing the pool of amyloidogenic precursor protein. These treatments have shown considerable efficacy in improving neurological symptoms, stabilizing cardiac function, and enhancing the quality of life for patients.

Beyond disease-modifying therapies, symptomatic management remains a critical component of care, addressing the diverse organ involvements. This includes medications for neuropathic pain, anti-diarrheals or prokinetics for gastrointestinal issues, management of orthostatic hypotension, and supportive care for heart failure. In selected cases, particularly before the advent of modern targeted therapies, organ transplantation played a significant role. Liver transplantation, which replaces the primary source of mutant TTR protein, was historically a viable option for early-onset forms of the disease, though its role has evolved with the availability of more effective pharmacological treatments. Heart transplantation may be considered for severe cardiac amyloidosis, often in conjunction with liver transplantation or other therapies, to address the systemic nature of the disease. Multidisciplinary care involving neurologists, cardiologists, nephrologists, gastroenterologists, and genetic counselors is essential for optimal patient outcomes.

## 6. Epidemiology and Geographic Distribution

While considered a rare disease globally, Familial Portuguese Polyneurotic Amyloidosis exhibits distinct epidemiological patterns and geographic concentrations. The highest prevalence rates are observed in populations with specific ancestral origins, most notably those from Portugal, Japan, and Sweden. The Val30Met (p.Val50Met) mutation is a classic example of a founder effect, where the mutation originated in a small ancestral population and then proliferated within geographically isolated communities. In northern Portugal, for instance, particularly in regions like Póvoa de Varzim and Vila do Conde, the prevalence can be as high as 1 in 538 individuals, making it one of the most common genetic diseases in these areas. Similarly, specific foci exist in regions of Japan (e.g., Nagano prefecture) and northern Sweden (e.g., Umeå region).

The global spread of FAP is largely a consequence of human migration and intermarriage patterns over centuries. While originating in specific regions, the disease has now been identified in diverse populations across the Americas, Europe, and other parts of Asia. As individuals carrying the *TTR* mutation migrate and establish new communities, the genetic predisposition to FAP is disseminated, leading to newly identified clusters and sporadic cases in what were previously non-endemic areas. This global dispersion complicates diagnosis, as healthcare providers in regions without known high prevalence may not readily consider FAP in their differential diagnoses, further contributing to diagnostic delays.

Despite its increasing recognition worldwide, the overall incidence of FAP remains low, estimated to be around 1 per 100,000 to 1 per 1,000,000 individuals globally, depending on the specific mutation and ethnic background. The variable age of onset and the phenotypic heterogeneity further challenge accurate epidemiological assessment. However, with improved diagnostic tools and increased awareness among medical professionals, particularly in light of emerging therapeutic options, the diagnosed prevalence is expected to rise. Understanding the epidemiological landscape is crucial for targeted screening efforts, genetic counseling, and ensuring equitable access to advanced diagnostic and therapeutic interventions for affected communities worldwide.

## 7. Debates and Future Directions

Despite significant advances, several debates and challenges persist in the field of Familial Portuguese Polyneurotic Amyloidosis. One major area of discussion revolves around the optimal timing of treatment initiation. Given the progressive nature of the disease and the irreversibility of advanced amyloid organ damage, early diagnosis and intervention are critical. However, the variable penetrance and expressivity of FAP make it challenging to predict which asymptomatic gene carriers will develop the disease and when, posing ethical dilemmas regarding presymptomatic treatment. Furthermore, the long-term efficacy and safety profiles of newer gene-

silencing therapies are still being continuously evaluated, and the potential for off-target effects remains a focus of ongoing research.

Research into novel therapeutic strategies is rapidly evolving, aiming to further improve outcomes for FAP patients. This includes the development of next-generation gene silencing agents with enhanced specificity and delivery mechanisms, as well as therapies targeting the removal or disruption of existing amyloid fibrils. Gene editing technologies, such as CRISPR-Cas9, are being explored as potential curative strategies to permanently correct the underlying genetic defect in the liver. Furthermore, efforts are underway to identify biomarkers that can accurately predict disease onset, monitor progression, and assess treatment response, allowing for more personalized and precise management strategies.

The importance of genetic counseling for individuals at risk and affected families cannot be overstated. Providing accurate information about inheritance patterns, risk assessment, and available testing options is crucial for informed decision-making. Ethical considerations surrounding presymptomatic genetic testing, particularly in pediatric populations, require careful navigation. Ongoing efforts are also focused on increasing global awareness of FAP among healthcare providers, especially in non-endemic regions, to reduce diagnostic delays and ensure that all affected individuals have access to prompt and appropriate care. Collaborative international research initiatives are vital for unraveling the remaining complexities of this debilitating disease and ultimately working towards a cure.

## Further Reading

Transthyretin amyloidosis - Wikipedia
Familial amyloid polyneuropathy - Orphanet
Transthyretin Amyloidosis (ATTR) - National Organization for Rare Disorders (NORD)
hATTR Amyloidosis - Amyloidosis Foundation