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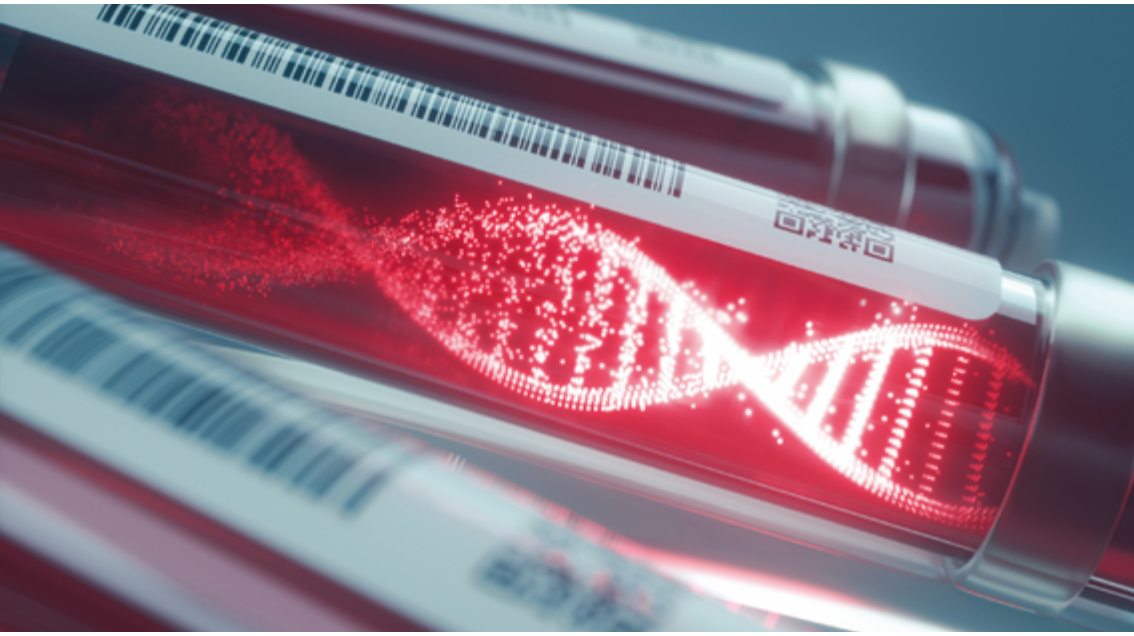


Hereditary transthyretin amyloidosis

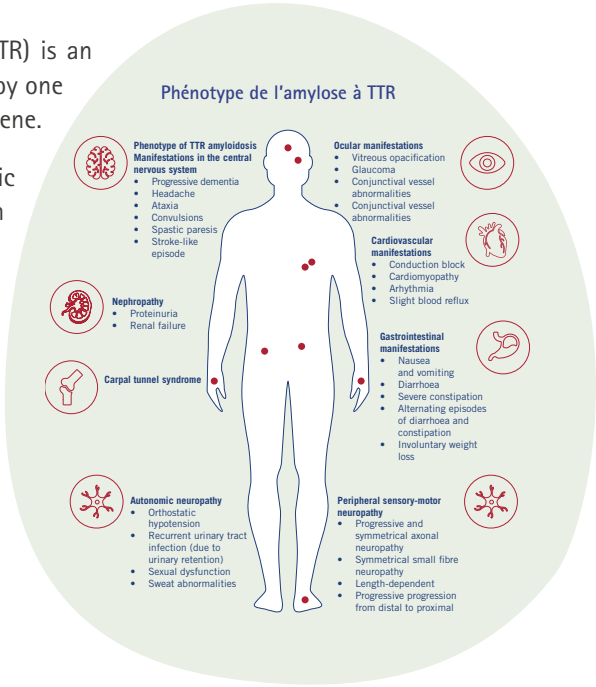
The contribution of long-read sequencing of the *TTR* gene for rapid and accurate diagnosis

Hereditary transthyretin amyloidosis (hATTR)

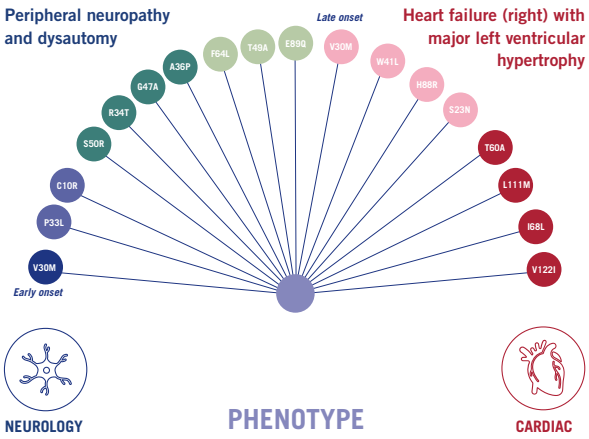
Hereditary transthyretin amyloidosis (hATTR) is an autosomal dominant disease. It is caused by one or more pathogenic variations in the *TTR* gene.

People with one or more pathogenic variations in the *TTR* gene produce an «abnormal» TTR protein throughout their lives. Amyloid deposits begin to form and then accumulate until they cause a chronic disease, mainly affecting the **nerves** and/or **heart**, and sometimes the **kidneys**, **eyes** and **synovial tissues** (tendons and ligaments).

Symptoms can appear at any time in early adulthood.



To date, there are more than **120 known pathogenic variants.**
Some favour neuropathy, others purely cardiac disease, or mixed forms, in some cases with renal and/or ocular involvement.



In clinical practice, the phenotypic variability of ATTR amyloidosis can make diagnosis complex.

Although rare, ATTR amyloidosis is a life-threatening disease, and **early diagnosis is vital.**

The most common forms of hATTR amyloidosis

Hereditary transthyretin amyloidosis is often referred to as **hereditary amyloid neuropathy** when the disease primarily affects the nerves - or f**amilial amyloid cardiomyopathy** when the disease primarily affects the heart.

Hereditary amyloid neuropathy

Hereditary amyloid transthyretin neuropathy is a rare (500 cases recorded in France), systemic, autosomal dominant disease resulting from pathogenic variants in the transthyretin (TTR) protein gene. It affects adults only.

The most frequent variation observed in France in hereditary amyloid neuropathies is **V30M (p.Val50Met)**. It is found in two-thirds of cases. However, other rarer variants such as S77Y and I107V may be encountered.

Familial amyloid cardiomyopathy

The prevalence of transthyretin-mutated cardiac amyloidosis is difficult to assess because the diversity of symptoms it causes makes it difficult to diagnose.
Certain transthyretin variants, which preferentially cause cardiac damage, are found in 0.4% to 3% of the population, depending on ethnic origin.
The V122I variant (p.Val142Ile) is the most common worldwide.

The diagnosis of these transthyretin pathologies is based on two main steps:

- **the identification of amyloid deposits :**
  - **for cardiomyopathy:** cardiac ultrasound (to look for MHC), ECG and NTproBNP/Tn assay (prognostic value) and Tc99m bone scan (specific for TTR amyloidosis).
  - **for neuropathy:** on nerve biopsy, immunostained for transthyretin
- **the identification of an amyloidogenic variation in the *TTR* gene by genetic analysis.**

Long-read sequencing in the diagnosis of hATTR amyloidosis

Long-read sequencing or third-generation sequencing makes it possible to produce significantly longer reads than second-generation sequencing (short-read), i.e. several thousand (or even millions) of base pairs vs. a few hundred (Fig.1 and 2).

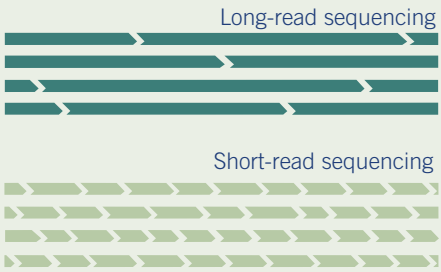


Figure 1 :

Genomescan

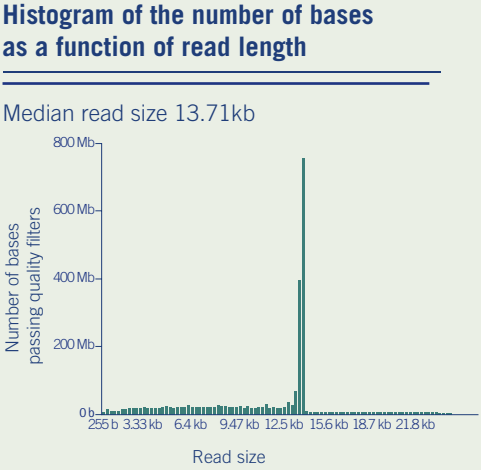


Figure 2 :

Read size: long fragments >10 kb

In hATTR amyloidosis, long-read sequencing offers a number of advantages, as it enables:

Sequencing of the entire *TTR* gene in a single analysis.

Save time and reduce diagnostic costs compared with a succession of targeted sequencing operations (exon by exon).

A diagnostic response **within 4 weeks.**

Clinical benefits

Identifying the responsible variation(s) makes it possible to:

- **Confirm or rule out the diagnosis of hATTR amyloidosis:**
  - Other conditions also present neuropathic symptoms similar to hereditary amyloid neuropathy, such as diabetic and alcoholic neuropathy, Charcot-Marie-Tooth disease and light chain amyloidosis.
  - From a cardiological point of view too, misdiagnosis is not unthinkable. hATTR should be excluded in patients with hypertrophic cardiomyopathy secondary to haemochromatosis, Fabry disease or cardiac sarcoidosis.
- **Provide prognostic information** on the pathology with regard to the variation detected.
- **Initiate therapeutic management as early as possible:** anti-amyloid treatment, symptomatic treatments if necessary, prevention and management of organ failure
- **Offer genetic counselling and family screening (for adults)**:
  - to detect subjects at risk of developing the disease early and offer them regular monitoring and effective treatment as soon as symptoms start,
  - or to reassure non-carriers once and for all.

Key points

- **Over 120 known pathogenic variants** in TTR amyloidosis.
- **The age of onset of the disease, the type of symptoms, the prognosis and treatment** depend on the variant responsible.
- Analysis of the *TTR* gene using long-read sequencing enables **the entire gene** to be studied in a single analysis, with results available **within 4 weeks.**
- The earlier the treatment is delivered, the more the progression of the disease can be delayed.

In practice

Test	Molecular study of the *TTR* gene using next-generation sequencing
Test code	TTR
Délai	4 weeks
Sample	5 mL EDTA whole blood or extracted DNA
Storage and transport	Refrigerated
Technique	Next generation sequencing
Price	Contact us
Required documents	• B12-INTGB test request form • Specific information sheet R76-INTGB available on www.eurofins-biomnis.com > Test guide > Test code: **TTR**

References

French National Protocol for Diagnosis and Care (Protocole National de Diagnostic et de Soins (PNDS)) - Cardiac amyloidosis. 2020-2021
French National Protocol for Diagnosis and Care (Protocole National de Diagnostic et de Soins (PNDS)) - Familial amyloid neuropathy. July 2022
Figure 1: https://www.genomescan.nl/long-read-sequencing-2/
Figure 2: Molecular study of the MEFV gene using Nanopore sequencing. Eurofins Biomnis.

For more information

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