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Original Research Article

CARDIOLOGY AND CARDIOVASCULAR MEDICINE

ISSN: 2572-9292

Impact of Epigenetics on the Development of Transthyretin Amyloid Cardiomyopathy: A Systematic Literature Review

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Abstract

Background: Transthyretin amyloid cardiomyopathy (ATTR-CM) is caused by deposition of variant or wild-type transthyretin in the heart. However, the impact of epigenetic modulation on the development of ATTR-CM is yet to be unveiled, warranting the need for a systematic review of the literature.

Methods: A systematic review of the literature was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic search was performed on PubMed and Embase databases on December 20th, 2024. Studies were selected based on the following predefined eligibility criteria: English-language studies or case series, including adult patients diagnosed with ATTR-CM, assessing the impact of epigenetics on the development of the disease. Relevant data were extracted to a predefined template. Quality assessment was based on the checklist by Newcastle – Ottawa Quality Assessment Scale for Case-Control Studies.

Results: From 170 records, 3 publications were selected, describing 3 case-control studies. Two studies evaluated DNA methylation and one assessed microRNA profiles. Both DNA methylation studies evaluated the hereditary form of ATTR amyloidosis (ATTRv). One study found an hypomethylation at cg09097335 in ATTRv carriers compared to controls, while the other study identified five hypomethylated sites in Val142Ile individuals with heart disease: cg06641417 (*FAM129B)*; cg26033908 (*SKI)*; cg14890866 (*WDR27);* cg15522719 (*GLS)*cg18546846 (RP11-550A5.2; intergenic). The study on microRNA profiling identified an upregulation of miR-339-3p in wild-type ATTR amyloidosis patients compared to controls. The limitations of these three studies do not allow to draw definitive conclusions.

Conclusions: This systematic review of the literature highlights the need for larger and well-balanced studies to evaluate the impact of epigenetics on the development of ATTR-CM.

Keywords: Transthyretin Amyloid Cardiomyopathy; Epigenetics; microRNA; DNA methylation; Hereditary

Background

Transthyretin amyloid cardiomyopathy (ATTR-CM) is characterized by the extracellular deposition of misfolded transthyretin (TTR) protein in the cardiac tissue, leading to thickening and stiffening of the myocardium [1,2]. It is the leading cause of restrictive cardiomyopathy and a recognized cause of morbidity and mortality [3].

TTR is a plasma protein predominantly produced in the liver, which circulates as a tetramer of four β-sheet rich monomers [2]. TTR amyloidosis

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Citation: Nuno Marques, Joana Apolónio, Isabel Palmeirim, Pedro Castelo Branco, Olga Azevedo. Impact of Epigenetics on the Development of Transthyretin Amyloid Cardiomyopathy: A Systematic Literature Review. Cardiology and Cardiovascular Medicine. 10 (2026): 15-21.

Received: February 12, 2026
Accepted: February 17, 2026
Published: February 25, 2026

Marques N, et al., Cardiol Cardiovasc Med 2026
DOI:10.26502/fccm.92920480

(ATTR) can be caused by the deposition of a mutant TTR due to pathogenic variants in the *TTR* gene (ATTRv) or deposition of the wild-type TTR protein (ATTRwt) [4].

ATTRv amyloidosis is inherited as an autosomal-dominant trait with variable penetrance and expressivity [5,6]. The *TTR* gene is found on chromosome 18, and more than 130 missense *TTR* amyloidogenic variants were identified [7]. The prevalence in Europe is estimated to be less than 1 in 100 000 individuals [8]. However, a study in the United Kingdom revealed that approximately 1 in 1000 individuals aged between 40 and 69 years was a carrier of a likely pathogenic or pathogenic *TTR* variant [9]. ATTRv amyloidosis has a variable age of onset, primary phenotypic expression and disease course, which are mainly determined by the specific *TTR* variant [10].

In ATTRwt amyloidosis, TTR becomes kinetically unstable, increasing its propensity to accumulate and deposit as amyloid fibrils. Its precise cause is unclear [2]. An age-related failure of homeostatic mechanisms promotes the dissociation of TTR into monomers, which subsequently misfold and aggregate to form amyloid fibrils that deposit in the heart [8,11].

Autopsy data show that 25% of the adults at ≥80 years of age have TTR amyloid deposits in the myocardium, with or without the presence of symptoms [12]. The CATCH study reported a prevalence of ATTRwt amyloidosis of 0.46% in individuals between 65 and 90 years from the general population, suggesting that this is not a rare disease [13].

ATTRwt amyloidosis almost always presents as a clinically isolated cardiomyopathy, usually being a late diagnosis, following the manifestation of severe cardiac symptoms due to amyloid deposition and advanced organ dysfunction [8].

The availability of specific therapeutic options for ATTR-CM underlines the need to predict the development of the disease. In fact, it has been suggested that the initiation of disease-modifying therapy should occur as early as possible, avoiding the accumulation of amyloid fibrils and irreversible organ damage, improving the quality of life and survival [14].

However, the epigenetic signatures of ATTR amyloidosis are poorly characterized, which limits our ability to identify unique markers to predict the development of ATTR-CM or provide guidance regarding the best timing for treatment [15].

Epigenetic mechanisms, including histones modifications, DNA methylation and regulation by non-coding RNAs (ncRNAs), can influence physiological and pathological processes by regulating gene transcription and/or expression [16] and are frequently deregulated in human diseases [15,17-20].

DNA methylation contributes to switch on-and-off gene transcription in the cell nucleus. By contrast, microRNAs (miRNAs), the best characterized group of ncRNAs, exert a fine- tuning post-transcriptional regulation by binding to the 3'-untranslated region (UTR) of their targets messenger RNA (mRNA) in the cytoplasm [16,21,22]. Notably, miRNAs and DNA methylation status are reversible, stable and measurable markers, detectable in tissues and biological fluids (e.g. blood, saliva, urine). As such, they are emerging as promising biomarkers and therapeutic targets in multiple diseases [18,19,22-25].

Herein, we provide a systematic review on the impact of epigenetics on the development of ATTR-CM.

Methods

This systematic review of the literature was performed using the methodology suggested by Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines [26]. It was conducted in 3 stages: a comprehensive and systematic search of the published literature to identify all potentially relevant studies; systematic selection of relevant studies based on explicit inclusion and exclusion criteria (Table 1); and extraction of relevant data from eligible studies to assess the role of epigenetic modifications on ATTR-CM.

Search Strategy

A systematic search was performed on December 20th, 2024, in the following databases: PubMed and Embase. The search was conducted in the English-language literature using the following keywords: "amyloidosis and epigenetic"; "amyloidosis and methylation"; "amyloidosis and microRNA"; "transthyretin and epigenetic". A deduplication step was performed to remove studies that overlapped among the databases.

Selection Criteria

To be included in this review, studies had to meet the predefined eligibility criteria listed in Table 1. In summary, this review included studies or case series on adult patients diagnosed with ATTR-CM that assessed epigenetic regulation (Table 1). A primary screening was performed by two authors who independently reviewed each reference (title and abstract) identified by the literature search, applied the inclusion and exclusion criteria listed in Table 1, and decided on whether to include or exclude the publication at that stage. Disagreement regarding the inclusion of studies was solved by a third author. The full-text articles were obtained for all potentially relevant studies identified by primary screening of titles and abstracts. These were independently reviewed by two reviewers against each eligibility criteria. Disagreement regarding the inclusion of studies was solved by a third author.

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Table 1: Inclusion and Exclusion Criteria of the Studies for Systematic Review.

Category	Inclusion criteria	Exclusion criteria
Population	• Patients with ATTR amyloidosis, either hereditary or wild-type Any ethnicity • Age ≥18 y	• Paediatric population (<18 y) • Absence of ATTR amyloidosis
Interventions	• Studies assessing epigenetic mechanisms	• Studies that do not assess epigenetic mechanisms • Genetic studies (e.g. on DNA mutations or SNP) are excluded if epigenetic study was not performed.
Outcomes	• ATTR-CM	• Outcomes not including ATTR-CM
Study design	• Observational or Interventional studies • Case Series ≥ 5 patients • Systematic reviews and/or meta-analyses	• Case reports • Case series < 5 patients • Preclinical studies • Reviews, letters, and comment articles
Language	• English	• Other than English

ATTR, transthyretin-related amyloidosis; CA, cardiac amyloidosis; SNP, single nucleotide polymorphism.

Data Extraction

The following data were extracted from the studies: (i) the epigenetic test performed in the study; (ii) the study design; (iii) the study sample; (iv) the study objective; (v) the main findings of the study; (vi) and the limitations referred by the authors of the study. The data extraction process was performed by one author to a predefined extraction data template (Table 2) and independently checked for errors against the original study report by another author. Multiple publications regarding the same patient population and reporting data for the same intervention were linked together and extracted as a single reference.

Table 2: Data extraction from the selected studies.

Study	Epigenetic mechanism	Type of study	Study sample	Objective	Main Findings	Limitations
De Lillo A et al. [15]	DNA Methylation	Case-control study	48 ATTRv carriers • 38 symptomatic • 10 asymptomatic o 33 Val50Met o 8 Phe84Leu o 3 Ile88Leu o 2 Ala140Ser o 1 Val142Ile o 1 rs36204272 o 32 healthy controls	Identify DNA methylation sites associated with ATTRv by comparing ATTRv affected patients, asymptomatic carriers and non-carriers.	• Hypomethylation at the cg09097335 site located in the *BACE2* gene body in ATTRv carriers. Significant differences between ATTRv symptomatic vs controls, $p=5{,}7x10^{-4}$; and ATTRv asymptomatic vs controls, $p=3{,}21x10^{-5}$). No difference between symptomatic and asymptomatic carriers. The difference exists in Val50Met patients and patients with other mutations vs controls. • Val50Met mutation disrupts the methylation site cg13139646 causing a drastic hypomethylation. • Significant methylation differences between symptomatic and asymptomatic Val50Met carriers at cg19203115 mapped in the *B4GALT6* gene.	• Small sample size. • Unbalanced age and sex between carriers and controls. • Need of further studies generating transcriptomic and epigenomic information. • Findings of disruption of the methylation site cg13139646 should be considered exploratory.
Pathak GA et al. [29]	DNA Methylation	Case-control study	96 Val142Ile carriers	Investigate the association of methylation changes with medical history of heart disease (HD) in TTR Val142Ile carriers.	o Five sites were hypomethylated in individuals with HD: o cg06641417 (*FAM129B*; logFC=−1.822; *P*perm=1.6×10−8) o cg26033908 (*SKI*; logFC=−1.615; *P*perm=1.7×10−8) o cg14890866 (*WDR27;* logFC=−2.028; *P*perm=3.0×10−8) o cg15522719 (*GLS;* logFC=−1.731; *P*perm=4.7×10−8) o cg18546846 (RP11-550A5.2; intergenic; logFC=−0.786; *P*perm=2.2×10−8)	• Small sample size • Unbalanced age between patients with HD and without HD

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Derda AA et al. [28]	MicroRNA	Case-control study	10 Healthy subjects 10 Patients with heart failure and LVEF<35% 13 ATTRv patients 11 ATTRwt patients	Identify differences in the circulating microRNAs profiles in patients with ATTRv and ATTRwt amyloidosis.	• ↑ miR-339-3p in ATTRwt patients (p=0,0347)	• Small sample size. • Unbalanced age of ATTRwt patients. • Does not reveal the pathomechanism of the upregulation of miR-339-3p in ATTRwt amyloidosis.

ATTRv, transthyretin-related amyloidosis variant; ATTRwt - transthyretin-related amyloidosis wild type; DNA – deoxyribonucleic acid; HD – heart disease.

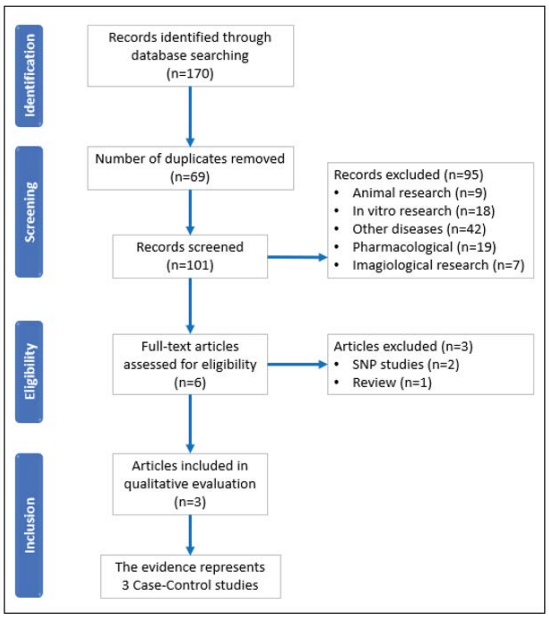
Quality Assessment

Quality assessment of the included studies was performed using a checklist by Newcastle – Ottawa Quality Assessment Scale for Case-Control Studies [27,28].

Results

Literature Selection

Database searches identified 170 records, of which 69 studies were duplicates and excluded. The screening of the remaining 101 studies led to the exclusion of 95 records, mainly because they were *in vitro* studies or studies conducted in animals, studies from other diseases or pharmacology studies. The remaining 6 records were further assessed for their eligibility for this review by full-text screening, which resulted in the additional exclusion of 3 publications, because two of them were single nucleotide polymorphism studies and one was a review article. Relevant data were then extracted from 3 publications, namely 3 case control studies reported in 3 articles. Figure 1 presents the PRISMA flow diagram of the studies identified in this systematic literature review.



SNP, single nucleotide polymorphism

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Included Studies and Quality Assessment

A total of 3 case-control studies were included in this review. The characteristics of these studies are presented in Table 2 and their quality assessment in Figure 2.

Item	Derda et al. [23]	De Lillo et al. [15]	Pathak et al. [29]
Selection			
Is the case definition adequate?	*	*	
Is the representativeness of the cases adequate?			
Is the selection of controls adequate?	*		
Is the definition of controls adequate?	*	*	
Comparability			
Comparability of cases and controls on the basis of the design or analysis is adequate for the main factor and any additional factor?	**	*	
Exposure			
What is the ascertainment of exposure?	*	*	
Same method of ascertainment for cases and controls?	*	*	
Is the non-response rate the same in both groups?	*	*	

Color Code: Green – Good quality; Yellow – Reasonable quality; Red – Poor quality

Note: A study can be awarded a maximum of one star for each item within the Selection and Exposure categories.

A maximum of two stars can be given for the Comparability category.

Figure 2: Quality Assessment with the Newcastle – Ottawa Quality Assessment Scale for Case-Control Studies.

Results of epigenetic studies

The data on epigenetic results that were extracted from the studies included in this review are detailed in Table 2.

DNA Methylation

This systematic review of the literature found two studies [15,29] that evaluated the impact of DNA methylation on ATTR amyloidosis.

The study by De Lillo et al. [15] included 48 ATTRv carriers (38 ATTRv affected patients and 10 asymptomatic ATTRv carriers) and 32 healthy controls. ATTRv individuals carried different *TTR* variants (33 Val50Met, 8 Phe84Leu, 3 Ile88Leu, 2 Ala140Ser, 1 Val142Ile and 1 rs36204272). In this study, an epigenomic-wide association study (EWAS) was conducted to identify DNA methylation sites associated with ATTRv amyloidosis [15].

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DOI:10.26502/fccm.92920480

The study found hypomethylation at the cg09097335 site located in the *BACE2* gene body in ATTRv carriers, with no significant difference between symptomatic and asymptomatic carriers.

This study also found that the Val50Met variant disrupts the methylation site cg13139646, causing a drastic hypomethylation at this site. This site co-methylates with the site cg19203115 mapped in the *B4GALT6* gene and a significant methylation difference also exists between Val50Met symptomatic and asymptomatic patients at the site cg19203115 in the *B4GALT6* gene [15].

The study of Pathak et al. [29] was a comparative study that included 96 Val142Ile African descendent carriers with or without medical history of heart disease [29]. In this study, the authors performed EWAS to identify the association of methylation changes with medical history of heart disease in Val142Ile carriers.

Five sites were reported to be hypomethylated in Val142Ile individuals with medical history of heart disease: cg06641417 (*FAM129B)*; cg26033908 (*SKI)*; cg14890866 (*WDR27);* cg15522719 (*GLS);* cg18546846 (RP11-550A5.2; intergenic) [29].

Functional protein interaction module analysis also identified an association between *ABCA1* module and medical history of heart disease. Target genes identified within the module were *ABCA1*, *SNTB2*, *BLOC1S2*, and *LIN7B* [29].

MicroRNA profiles

This systematic literature review found one study [23] that evaluated microRNA profiles in ATTRv and ATTRwt amyloidosis.

The study by Derda et al. [23] was a comparative study that included 10 healthy subjects, 10 patients with heart failure and left ventricular ejection fraction <35%, 13 ATTRv patients and 11 ATTRwt patients. This study aimed to identify differences in the circulating microRNAs profiles in patients with ATTRv and ATTRwt amyloidosis. The study identified an upregulation of miR-339-3p in ATTRwt patients compared to controls [23].

Discussion

This systematic literature review found three studies that evaluated epigenetic regulation in ATTR amyloidosis, two on DNA methylation [15,29] and one on microRNAs [23], but all had significant limitations, preventing any definitive conclusions.

The two studies of DNA methylation only evaluated ATTRv amyloidosis [15,29]. Notably, this systematic review of the literature did not identify any studies on DNA methylation evaluating ATTRwt amyloidosis.

The study of De Lillo et al. [15] found an hypomethylation at the site cg09097335 located in the *BACE2* gene body in ATTRv carriers (symptomatic and asymptomatic) [15]. Beta-secretase 2 (BACE2) cleaves the amyloid-beta precursor protein (APP) to amyloid-beta in the brain, but it is also present in peripheral tissues affected by amyloidosis acting in the inflammatory response. The authors speculate that there might be a link between BACE2 and TTR-induced inflammation in the tissues [15].

The study also found that the Val50Met mutation disrupts the methylation site cg13139646, causing a drastic hypomethylation in carriers. This site co-methylates with the site cg19203115 mapped in the *B4GALT6* gene, and this gene exhibited a significant methylation difference between Val50Met symptomatic and asymptomatic carriers. Interestingly, the *B4GALT6* gene encodes an enzyme also involved in inflammatory processes in the tissues [15].

However, the study by De Lillo et al. [15] presents several limitations. The study had a small sample size and included several *TTR* variants associated with different phenotypes. As the analysis of DNA methylation was carried out in a grouped manner for all variants, no conclusions could be drawn regarding the development of ATTR-CM or any other specific ATTR manifestation, nor regarding specific *TTR* variants, with the exception of the most prevalent variant in the sample, the Val50Met variant, which was individually analyzed [15].

In addition, there was a significant unbalance between carriers and controls regarding factors relevant to epigenetic analysis, such as age and sex, although it should be noted the attempt of the authors to adjust the results to the impact of these factors and others that significantly affect DNA methylation, such as smoking habits [15].

On the other hand, Pathak et al. [29] identified five sites that were hypomethylated in Val142Ile carriers with medical history of heart disease: cg06641417 (*FAM129B)*; cg26033908 (*SKI)*; cg14890866 (*WDR27);* cg15522719 (*GLS)*; cg18546846 (RP11-550A5.2; intergenic) [29]. In addition, functional protein interaction module analysis also identified an association between *ABCA1* module and medical history of heart disease. Interestingly, the identified genes are involved in transport and clearance of amyloid deposits (*GLS*, *ABCA1*, *FAM129B*), cardiac fibrosis (*SKI*) and muscle tissue regulation (*SKI*, *FAM129B*) [29].

However, the study of Pathak et al. [29] has limitations, namely the absence of a healthy control group, which limits the interpretation of the results. The study also lacks precision in the definition of heart disease, as self-referred heart disease is used for this categorization. Characterization of the groups of carriers with and without medical history of heart disease is also lacking, particularly regarding the characteristics that are usually associated with DNA methylation changes.

The authors also report some unbalance between the groups with respect to age, which is also a main factor that affects DNA methylation. In addition, the study is focused only on Val142Ile individuals, so the results cannot be extrapolated to individuals of European descent, carriers of other *TTR* mutations or wild type ATTR amyloidosis [29].

Finally, the study by Derda et al. [23] was the only evaluating the microRNA profile in ATTR amyloidosis and the only epigenetics study assessing ATTRwt individuals.

The study identified an upregulation of miR-339-3p in ATTRwt patients compared to controls, but the authors were unable to provide an explanation for the involvement of this microRNA in the pathomechanism of ATTRwt amyloidosis [23]. Moreover, the study had a small sample size, preventing any conclusive results for ATTRv or ATTRwt amyloidosis. Clinical manifestations of ATTR patients were not characterized and the presence and type of cardiac manifestations were not specifically provided. The specific *TTR* mutations of ATTRv carriers were also not reported. In addition, there was a significant unbalance between amyloidosis patients and controls regarding factors relevant to epigenetic analysis, such as age and sex [23].

Conclusion

This systematic review of the literature found three studies that evaluated the epigenetics of ATTR-CM, two evaluating DNA methylation [15,29] and one evaluating microRNA profiling [23]. These studies identified some potential candidate epigenetic biomarkers for ATTR-CM, but the limitations of the studies prevent to draw any definitive conclusions. Larger and better-balanced cohorts of patients and controls should be investigated in the future.

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Citation: Nuno Marques, Joana Apolónio, Isabel Palmeirim, Pedro Castelo Branco, Olga Azevedo. Impact of Epigenetics on the Development of Transthyretin Amyloid Cardiomyopathy: A Systematic Literature Review. Cardiology and Cardiovascular Medicine.10 (2026): 15-21.