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# Is Hereditary Transthyretin Amyloidosis the Third Leading Cause of Monogenic Chronic Kidney Disease, Only Behind ADPKD and Alport Disease?

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We have read with great interest the results of the article by Bleyer et al. [1] showing that a broad panel genetic testing with 382 genes associated with kidney disease identified a monogenic cause in 21.1% (212/1007) of cases with chronic kidney disease (CKD). Positive results permitted to diagnose autosomal dominant polycystic kidney disease (ADPKD) (PKD1 [34.1%] and PKD2 [10.0%] genes), Alport syndrome (COL4A5 [10.9%], COL4A4 [6.4%], and COL4A3 [5.9%] genes), and transthyretin amyloidosis (ATTR) (TTR gene [4.1%]). Regarding the latter, all patients presented a variant c.424G>A (p.Val142Ile) in the TTR gene (formerly known as Val122Ile; [rs76992529]) which is reported in the European population with a frequency of 0.004432% while in the African descent population with a frequency of 1.5–3.5% [2, 3], with a not already completely defined penetrance. Interestingly, a recent study conducted whole exome sequencing, searching for monogenic causes of CKD among a cohort of 114 adults with familial CKD but did not identify any TTR mutation, although 35.6% of the patients reported having non-European ancestry [4].

ATTR is caused by the systemic extracellular deposition of transthyretin amyloid fibrils in different organs and can be hereditary (hATTR), due to mutations in the TTR gene, or wild-type ATTR, due to age-related TTR misfolding abnormalities. The hATTR is the most common form of hereditary amyloidosis and is characterized by an autosomal dominant transmission with heterogeneous clinical presentations that vary according to the specific TTR gene mutation. By the time, more than one hundred causative mutations have been described, mostly showing a prevalent neurological, cardiac, or mixed phenotype. Different clinical phenotypes include polyneuropathy, restrictive cardiomyopathy, tenosynovial involvement, and more rarely, renal and ocular involvement.

Renal involvement in hATTR occurs much less frequently and could be associated with either a cardiorenal syndrome or a direct amyloid deposition and, depending on whether we consider only the direct mechanism of damage or both, may range from 4.3% [5] to 37% [6] of patients with hATTR. In the first case (indirect mechanism), as seen in other forms of cardiorenal syndrome

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**Table 1.** Renal involvement in hATTR

| Centers involved | Patients with hATTR | Patients with renal injury | Patients with "possible" renal hATTR *(renal injury not related to any other disease)* | Patients with biopsy-proven renal hATTR |
|---|---|---|---|---|
| Policlinico S. Orsola Bologna | 50 | 11 | 7 | **1** |
| AOU Careggi Firenze | 66 | 24 | 8 | **0** |
| Fatebenefratelli Hospital Roma | 49 | 9 | 3 | **0** |
| Total | 165 | 44 | 18 | **1** |

like wild-type ATTR [7], renal involvement is generally characterized by a stage 2-3 CKD and absent or mild proteinuria.

In the second case (direct mechanism), renal injury outbreaks with microalbuminuria, progressing towards overt proteinuria and later renal failure [8], which in one third of patients progresses to end-stage kidney disease in about 10 years [9]. This renal phenotype was associated with about 15 different TTR gene mutations, of whom Val30Met is the more common [10]. Apart from the disease associated with the Val30Met mutation, which is particularly prevalent in Portugal, kidney involvement of hATTR is not well characterized and has been poorly studied.

Specifically, the c.424G>A (p.Val142Ile) variant is currently recognized as the most common cause of hereditary amyloid heart disease worldwide [2, 3, 11]. Although the Val142Ile mutation was also described in association with a biopsy-proven renal TTR amyloid deposition [12], almost all patients with the Val142Ile mutation showed an isolated late-onset cardiomyopathy, a phenotype widely described in scientific literature [2, 13, 14], suggesting a potential secondary renal injury related to a cardiorenal syndrome.

We would really appreciate if Bleyer et al. could provide relevant data regarding the detection of TTR amyloid deposits from renal biopsies as an expression of the direct causal relationship between TTR gene mutation and CKD in their cohort of patients with hATTR due to the Val142Ile mutation, if such data is available.

We investigated the frequency, characteristics, and distribution of the renal phenotype of hATTR in our country through a multicenter, retrospective, observational study involving three Italian referral centers for ATTR. This survey was based on a specific questionnaire on renal involvement in patients with hATTR, concerning the number of patients carrying TTR mutations, the types of mutations observed, characteristics of renal injury (24 h urinary protein excretion, albuminuria, renal function, date of onset of disease), potential confounding comorbidities, and if a renal biopsy was performed. In the absence of a renal biopsy, all patients who showed a renal injury not attributable to any other coexisting disease (such as diabetes mellitus, glomerulonephritis, or cardiorenal syndrome without detectable proteinuria) were classified as doubtful/possible cases of renal hATTR. Mass spectrometry-based proteomic analysis of organ biopsies and/or genetic analysis allow amyloid typing and accurate amyloidosis diagnosis. In our study, all patients with a suspected diagnosis of hATTR amyloidosis [(1) people with symptoms raising a possibility of hATTR amyloidosis and/or a positive Tc-DPD scan; (2) people with biopsy-confirmed ATTR amyloidosis] underwent genetic testing using whole-exome sequencing.

We recruited a total of 165 symptomatic patients affected by hATTR, with 34 different TTR gene mutations (Table 1). Overall, 44 out of 165 (27%) patients showed a CKD defined as eGFR<60 mL/min (calculated using the CKD-EPI creatinine formula) and/or the presence of a variable degree of proteinuria (albumin-to-creatinine ratio >300 mg/g, proteinuria ≥30 mg/dL, and/or >0.3 g/24 h). Among them, 18 (11%) patients showed a renal injury not attributable to any known disease and were considered as possible renal involvement secondary to the TTR mutation. In one case, the renal biopsy showed the presence of TTR amyloid deposits; this patient presented a Val30Met mutation and developed CKD at 43 years of age. In other 4 cases, renal biopsy identified different nephropathies (in particular, membranous nephropathy in 2 cases).

We identified a cohort of 10 out of 165 patients with hATTR due to the Val142Ile mutation, with available information on renal function and proteinuria. All the patients showed European ancestry, a late-onset cardiomy-

opathy (associated with tenosynovial involvement in 5 and peripheral neuropathy in one), NYHA class ≥3 in 50% of cases, a long previous history of hypertension, and an average of 1.6 previous hospitalizations for decompensated heart failure. The mean age at diagnosis was 75.1 years, with a mean serum creatinine of 1.14 mg/dL and eGFR of 69.3 mL/min/1.73 $m^2$. Among them, 6 patients showed CKD (defined as eGFR <60 mL/min and/or the presence of proteinuria), but only one patient had proteinuria unrelated to any other disease. In fact, 3 patients were affected by type 2 diabetes mellitus (only one with overt proteinuria), and 8 out of 10 patients were affected by cardiorenal syndrome type 1 or type 2, due to severe chronic heart failure or previous decompensated heart failure episodes. These data may support the hypothesis that only about 10% of hATTR patients experience direct renal involvement.

Two studies reported a prevalence of CKD of 15% and 37% in patients with hATTR carrying diverse mutations [15, 16] while, in a recent study on a French cohort, 24 out of 79 (30.4%) symptomatic patients with hATTR developed CKD [17]. Authors reported that not all TTR mutations were equal in terms of kidney involvement, and the Val122Ile seemed particularly at risk of CKD (OR 57.2 [6.5–7,540]). However, data on kidney impairment in hATTR are variable in the literature and this could be explained by (1) different adopted definitions of CKD, (2) heterogeneous prevalence of different mutations, (3) absence of kidney biopsy-based studies, and (4) potential coexisting role of APOL1 gene variants (especially in the African descent population).

Our data showed that renal involvement in hATTR is apparently uncommon in our country, and the underlying etiopathogenetic mechanism is cardiorenal syndrome without detectable proteinuria in most of the hATTR patients with CKD. However, our data (similarly to other published studies) may be the results of an underdiagnosis either due to the unsystematic use of renal biopsy. A further explanation may be a possible different clinical expression of TTR gene variants in our country. Although renal biopsy is not routinely required, it might be recommended when determining the indication for tafamidis, patisiran, or inotersen treatment in hATTR amyloidosis patients.

## Statement of Ethics

The study was approved by the Local Ethics Committee (study approval number is 19212/oss) and is in accordance with the principles of the Declaration of Helsinki. Due to the retrospective nature of this study, informed consent was waived for patients who had died or were lost to follow-up. Otherwise, all subjects provided written informed consent that was approved by the Institutional Review Board.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


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## Author Contributions

Marco Allinovi, Federico Perfetto, and Franco Bergesio designed the research and analyzed and interpreted the data. Marco Allinovi, Francesco Cappelli, Maria Grazia Chiappini, Marisa Santostefano, Alessia Argirò, Tullio Catalucci, Mattia Zampieri, Federico Perfetto, and Franco Bergesio contributed to data collection and performed the research. Marco Allinovi, Franco Bergesio, Alberto Parise, and Federico Perfetto wrote the paper. Alberto Parise, Maria Grazia Chiappini, and Marisa Santostefano critically reviewed the manuscript. All the authors read and approved the final manuscript.

## Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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