# Autosomal Dominant Nephritis with Renal Failure of Non-Alport Type: Clinical And Molecular Studies

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**Key words:** familial nephritis, renal failure, autosomal dominant type

## Abstract

**Background:** Familial nephritis is a heterogeneous group of disorders caused by several genetic conditions such as Alport syndrome, glomerulonephritic syndromes, and unclassified nephritis without deafness or ocular defects.

**Objectives:** To describe a family of Iraqi Jewish origin, several of whose members suffer from non-syndromic renal failure without deafness or ocular defects and where transmission is by autosomal dominant inheritance. We present the case histories of four family members and describe the molecular analysis performed in order to seek a possible linkage to one of the genes causing Alport or Alport-like syndromes.

**Methods:** We investigated all family members over the age of 18 for evidence of renal failure. We also extracted DNA and carried out molecular linkage analysis with polymorphic markers in each of the known loci involved in Alport and Alport-like syndromes.

**Results:** Histology of the renal biopsy specimens showed non-specific findings. Linkage was excluded for all the Alport and Alport-like syndrome loci.

**Conclusions:** The condition suffered by several members of this family seems to represent a unique autosomal dominant type of progressive hereditary nephritis, characterized by hypertension and progressive renal failure without significant hematuria or proteinuria. The main histological changes are non-specific in the early stage of the disease. Our study rules out all the currently known genes that cause Alport syndrome as being responsible for the basic defect in this type of nephritis.

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Familial nephritis is a heterogeneous group of disorders caused by several genetic conditions such as Alport syndrome, glomerulonephritic syndromes, and unclassified nephritis without deafness or ocular defects. We report on a family of Iraqi Jewish origin, several of whose members suffer from non-syndromic renal failure without deafness or ocular defects and where transmission is by autosomal dominant inheritance. This family seems to represent a new type of nephritis leading to renal failure, which is not linked to any of the previously mapped genes causing Alport syndrome.

## Patient Descriptions

This family includes 16 affected members over four generations [Figure 1]. We investigated all the family members who were over 18 years old for evidence of renal failure, and found that 10 individuals currently had end-stage renal failure that had developed between the ages of 18 and 38. Five of these have undergone renal transplantation. We also found four affected individuals who did not have end-stage renal failure. Two family members have died as a result of end-stage renal failure. The clinical characteristics of the 14 surviving affected family members are summarized in Table 1.

### Patient III-3

This 28 year old patient, as part of the preparation for donating a kidney to his brother, underwent blood tests and was found to

**Table 1.** Summary of the clinical characteristics in the surviving affected members of the family

| Patient | Age at onset | Clinical signs at onset | Age at end-stage renal failure |
|---|---|---|---|
| II-3 | 38 | End-stage renal failure | 38 |
| III-1 | 28 | End-stage renal failure | 28 |
| III-2 | 26 | End-stage renal failure | 26 |
| III-3 | 28 | Raised creatinine and blood pressure | 38 |
| III-4 | 38 | Raised creatinine (2.8 mg/dl) | NY |
| III-8 | 33 | End-stage renal failure | 34 |
| III-10 | 34 | Raised creatinine and hypertension | 40 |
| III-12 | 26 | End-stage renal failure | 30 |
| III-14 | 30 | Raised creatinine (1.5 mg/dl) | 37 |
| III-16 | 34 | Raised creatinine and hypertension | NY |
| III-17 | 26 | Raised creatinine and hypertension | 32 |
| IV-2 | 18 | Raised creatinine and hypertension | NY |
| IV-7 | 25 | Raised creatinine and hypertension | NY |
| IV-8 | 18.5 | End-stage renal failure | 30 |

NY = not yet

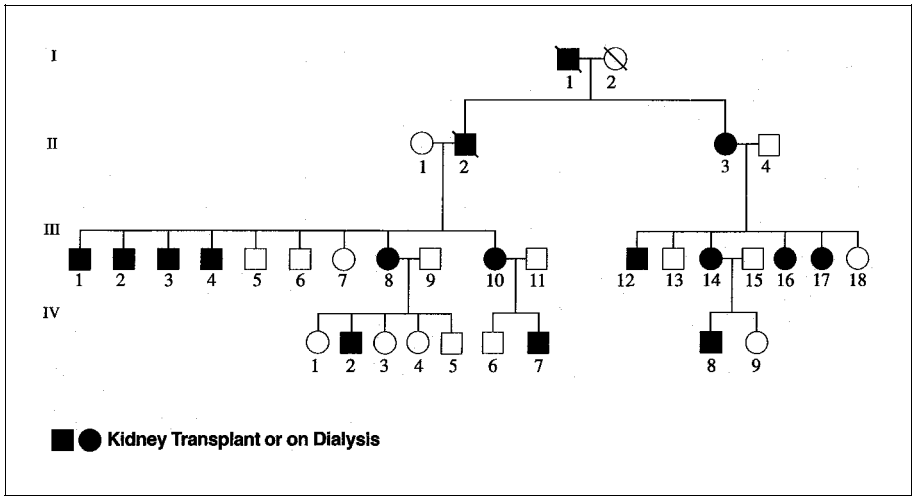


**Figure 1.** Pedigree of Iraqi Jewish family with autosomal dominant nephritis.

have a high serum creatinine level. His blood pressure was also markedly elevated. Renal ultrasound, however, was normal and urine analysis showed no evidence of either hematuria or proteinuria. At recent follow-up, at the age of 38, his serum creatinine level was 6 mg/dl and blood pressure 160/110. He is receiving medication for the hypertension, but compliance is poor.

Twenty-four hour urine analysis (2,100 ml) at this time yielded the following results: protein 147 mg/24 hours (normal range 30–150), creatinine clearance 10.6 ml/min, uric acid 256.41 mg/24 hr (range 200–1,000), phosphorus 0.4 g/24 hr (range 0.3–1.0), sodium 107.94 mEq/24 hr (range 30–300), potassium 37.8 mEq/24 hr (range 26–123), and calcium 30.03 mg/24 hr (range 100–300). He is presently undergoing peritoneal dialysis.

### Patient III-17

At the age of 26, this patient was found to have a high serum creatinine level (1.5 mg/dl) and elevated blood pressure (150/110). Renal ultrasound and renal isotope testing were normal. At the age of 32 years she developed end-stage renal failure and underwent renal transplantation.

### Patient III-4

Two years ago, at the age of 38, this patient was found to have a high serum creatinine level (2.8 mg/dl) and elevated blood pressure. Although his serum creatinine level is presently 3.2 mg/dl, recent urine analysis showed no evidence of either hematuria or proteinuria.

### Patient III-16

Prior to commencing a new job, this patient recently underwent tests that revealed a high serum creatinine level (3.1 mg/dl). All the other tests gave normal results.

### Other clinical findings

All the affected family members have normal hearing, and eye examinations were normal. There were no abnormal physical findings. Renal ultrasound examination in all the affected individuals did not reveal any abnormalities.

### Renal biopsy

Renal biopsy was performed in two individuals (III-17 and III-2). Slides are only available for individual III-17, who was 26 years old when the biopsy was carried out. At that time blood pressure was 150/110 and serum creatinine level 1.7 mg/dl. Electron microscopy, apart from showing mild thinning of the basement membranes [Figure 2], detected no significant renal abnormalities in seven glomeruli or in the medulla, nor were any abnormalities seen after immunofluorescence staining for IgG, IgA and IgM, C3, C4, C1q, properdin, fibrinogen, and albumin. Light microscopic pictures are not available, but these did show normal histology. Individual III-2 underwent renal biopsy at age 27, when blood pressure was 160/110 and serum creatinine level 1.4 mg/dl. Only the histological report is available, which notes that of 10 glomeruli examined 7 were normal and 3 were sclerotic, and there was evidence of interstitial fibrosis and mild tubular atrophy. These findings of renal failure with normal urine suggest that the features present in the members of our reported family are typical of tubulo-interstitial disease.

### Molecular studies

***Genotyping.*** DNA (from all the living family members in Figure 1) was extracted from whole blood according to standard phenol-choloroform protocol. A possible linkage to one of the genes causing Alport and Alport-like syndromes was studied (COLA3 and COLA4 on chromosome 2, COLA1 and COLA2

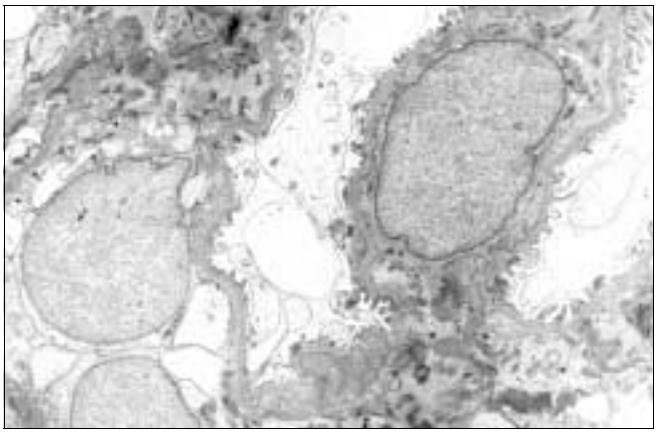

**Figure 2.** Thinning of the glomerular basement membrane with a mean width of 155 nm, demonstrated by multiple measurements. (x 3,300)

on chromosome 13, and a candidate locus for Alport-like syndrome on chromosome 22). For each candidate gene we selected 4–6 polymorphic markers: D2S396, D2S2297, D2S1363, D2S1370 for COLA3 and COLA4; D13S796, D13S779, D13S261, D13S1265, D13S285 for COLA1 and COLA2 (Genome database), and D22S283, D22S691, D22S685, D22S281, D22S689, D22S1167 for chromosome 22 [1].

Polymerase chain reaction was done in a 15 µl reaction volume containing 150 ng of genomic DNA, 10 pmol of each primer, 1.5 mM dNTPs (dCTP depleted), 0.1 µCi $dCTP^{32}$, 1.5 mM $MgCl_2$, 0.5 U Taq polymerase (Bioline UK), and PCR buffer containing 160 mM $(NH_4)SO_4$, 670 mM Tris HCl (pH 8.8), and 0.1% Tween 20. After an initial denaturation for 5 minutes at 94°C, 35 cycles were performed (94°C for 30 seconds, 55°C for 30 sec, and 72°C for 30 sec), followed by final extension time for 5 min at 72°C. Samples were mixed with 10 µl of loading buffer, denatured at 94°C for 3 min and electrophoresed on 6% denaturing polyacrylamide gel. Linkage was excluded for all the genes tested, thus ruling out these genes as the genetic cause of the nephritis in this family.

## Discussion

The condition suffered by several members of the family studied represents a unique autosomal dominant nephritis without deafness or ocular findings. This is a severe disease that usually results in end-stage renal failure. Of the 14 surviving patients 10 developed end-stage renal disease, which was already evident in 6 of them at presentation. However, in contrast to the clinical course, there were very few clinical findings other than elevated blood pressure and gradually increasing serum creatinine levels. Microscopic hematuria and mild proteinuria may occur after end-stage renal failure develops.

Autosomal dominant nephritis without deafness or ocular findings (OMIM: 161900) has been reported by several investigators [2–4]. Among families with familial nephropathy, another Israeli family of Iraqi Jewish origin with similar clinical findings has been reported [2]. In this family, 20 affected individuals were identified among 66 family members who were examined. The affected individuals showed similar clinical findings to those in the patients described here, except that they also had mild proteinuria. Renal biopsy in four patients in the family showed normal histology in one, chronic glomerulonephritis in two, and pyelonephritis with nephrosclerosis in the fourth. The authors concluded that the histological studies were too limited and inconsistent to warrant a conclusive pathologic diagnosis. Similar to the findings in our family, hypertension was present 3–11 years prior to renal failure. Thus, the possibility of hypertension being causative rather than secondary to underlying renal disease could not be determined.

In our family study, histological examination in one of the affected individuals who underwent renal biopsy (at age 26) did not reveal specific changes in the early stage of the disease apart from mild thinning of the basement membranes. In the other individual, aged 27, histology showed that of 10 glomeruli examined 7 were normal and 3 were sclerotic, and there was evidence of interstitial fibrosis and mild tubular atrophy. Unfortunately, we were not able to confirm these findings in other affected individuals in this family. The thin basement membrane in one of these patients differs from that in previously reported hereditary nephritis, including the family presented by Richmond et al. [5]. In their family study, light microscopy and electron microscopic studies in end-stage renal failure demonstrated the basement membrane thickening seen in other progressive forms of hereditary nephritis. It is possible that the thin basement membrane found in our patient (III-17) is typical only of the early stage, with more significant involvement of the interstitial component occurring in later stages. Alternatively, the pathological changes seen in our family represent a unique type responsible for progressive hereditary nephritis.

The inherited diseases of the glomerular basement membrane include thin basement membrane disease nephropathy, nail patella syndrome, and Alport syndrome. Typically, in familial thin basement membrane nephropathy a thin basement membrane can be seen [6]. This condition, characterized by persistent microhematuria and a relatively good prognosis, rarely develops into end-stage renal failure. In contrast, as described above, no microhematuria was seen in our patients. The ultrastructural changes in Alport syndrome include a thin and split basement membrane, but of a lesser degree of severity than that found in FTBMN. This is usually associated with proteinuria, as well as sensorineural hearing loss and ocular defects.

Of note is the molecular analysis of our family study. To the best of our knowledge, this is the first time that progressive hereditary nephritis without hearing loss or ocular abnormalities has been studied for possible linkage to one of the genes that causes Alport syndrome. Our study has excluded these as being responsible for the basic defect in the progressive hereditary nephritis in our family.

The condition suffered by several members of the family seems to represent a unique autosomal dominant type of progressive hereditary nephritis, characterized by hypertension and progressive renal failure without significant hematuria or proteinuria. The main histological changes are non-specific in the early stage of the disease. Our study rules out all the currently known genes that cause Alport syndrome as being responsible for the basic defect in this type of nephritis. Further whole-genome linkage studies in this informative family will allow identification of the basic defect.

PCR = polymerase chain reaction

FTBMN = familial thin basement membrane nephropathy

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