New Familial Cases of Karyomegalic Interstitial Nephritis With Mutations in the *FAN1* Gene

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Abstract

Karyomegalic interstitial nephritis (KIN) is a rare disease entity that was first described by Burry in 1974 and given this term by Mihatsch 1979 and al five years later. KIN is characterized by chronic tubulo-interstitial nephritis associated with enlarged tubular epithelial cell nuclei, which leads to progressive decline of renal function. The prevalence of this disease is less than 1% and its pathogenesis is unclear. KIN results from the mutation in the *FAN 1* (FANCD2/FANCI-Associated Nuclease 1) gene, a gene involved in the DNA damage response pathway, particularly in the kidney. KIN seems to be rather multifactorial involving an environmental factor Ochratoxin A (OTA) but especially a genetic predisposition.

In this article, we report 6 additional cases of KIN with histological evidence in 3 patients. Family clustering and differences in susceptibility to develop the nephropathy in spite of a high OTA contamination in all subjects show that there is a genetic susceptibility. So we completed our explorations by a genetic study. This study allowed us to identify novel mutations in the *FAN1* gene in the affected members. To our best knowledge, this is the first Tunisian study involving familial cases of KIN with mutations on the *FAN1* gene.

Introduction

Karyomegalic interstitial nephritis (KIN) is a rare disease that was first described by Burry in 1974 [1] and given this term later by Mihatsch and al in 1979 [2]. A history of recurrent respiratory infections and progressive renal failure was described. Since then, approximately 50 cases of KIN have been reported. KIN is characterized by chronic tubulo-interstitial nephritis associated with enlarged tubular epithelial cell nuclei, leading to progressive decline of renal function. Its prevalence is below 1%. Its pathogenesis is unclear yet.

Current data refer to OTA as the most likely causative etiologic factor [3]. Differences in disease susceptibility can be caused by genetic polymorphisms of enzymes and transporters involved in toxicokinetics of OTA. A familial clustering was suspected and frequency of human leukocyte antigen HLA-A9 and HLA-B35 haplotypes suggested a genetic susceptibility [4]. Recently, mutations in the *FAN1* gene involved in the DNA damage response pathway, including the kidney, have been reported as causative in familial cases of KIN [5]. These findings allowed us to highlight the potential link between defective DNA repair and chronic kidney disease progression. In this paper we report 6 additional cases of KIN with histological evidence in 3 patients, in whom we identified mutations in the *FAN1* gene.

Subjects And Methods

Subjects

Patients of two consanguineous families from the north of Tunisia, Family A and Family Z, (Figure 1) were referred to the nephrology department because of impaired renal function. KIN was diagnosed and etiological study of this nephritis was carried out.

Family A

In family A, the siblings were composed of 9 members. Two of them had KIN confirmed by renal biopsy and 2 others had end-stage renal disease (ESRD) due to tubulo-interstitial nephropathy.

Family Z

The second family was living in urban areas. The sibling was composed of 3 brothers and 1 sister. One of them had KIN confirmed by renal biopsy and the other brother had ESRD due to tubulo-interstitial nephropathy.

In view of the similar histological findings in family A and Z and according to the family clustering of KIN described in the literature, it seemed that it was the same nephropathy in the 4 siblings of family A and the 2 others of family Z. Genetic factors was necessary for disease onset. We performed clinical examination, laboratory investigation and genetic study for the whole families.

Informed consent was obtained from all family members.

Methods

Genotyping of CYP3A4*18 and GSTP1 using PCR-RFLP

Using the PCR-RFLP method according to Ruzilawata et al. [6] and to Soya et al. [7], DNA samples were investigated respectively for the CYP3A4*18 mutations and the GSTP1 polymorphism.

Sequencing

DNA was extracted from peripheral blood using standard method for individuals II-2, III-1, III-2, III-3, I-4 and II-8 of family A and for individuals I-1, I-2 and II-3 of family Z (Figure 1)

The 13 coding exons of the *FAN1* gene were amplified according to the PCR protocol described by Zhou et al. [5].

Sequencing results were visualized and data were analyzed using Sequencher 5.0 Demo. Three prediction programs (Polyphen-2 software, SIFT, Varsome) were used to predict the functional effect of the variations detected.

Results

Family A

The 4 affected subjects were male with mean age at renal disease diagnosis of 33 years and mean age of the onset of the ESRD of 36 years. Three were farmers and lived in rural areas. There was no history of recurrent respiratory infection, nor exposure to heavy metals, alkylating agents or irradiation. Physical examination was normal for all subjects except urinary tests. Proteinuria 1+ was noted in 7 cases, and 2+

in 2 cases. Leucocyturia was found in 15 cases. All of these cases were unknown to have nephropathy. Laboratory investigations showed hepatic cytolysis and cholestasis in our 4 patients. Moreover, HLA typing found the A23 and A24 alleles. These same antigenic specificities were also found in two healthy subjects. Liver biopsy performed in patient IV-7 showed no specific pathology.

Kidney biopsy was performed in 2 patients (IV-7, IV-12) who had mild renal failure. Anathomopathology examination revealed karyomegalic tubulo-interstitial nephritis (Figure 2)

Family Z

Family Z consisted of 8 subjects. Renal biopsy was performed in patient II-3 and showed KIN (Figure 3). He was 25 years old man. His brother was in ESRD at the age of 31.

Urine dipstick test and blood pressure of the other family members were normal. Liver function test did not reveal cytolysis nor cholestasis.

Genetic study

Detection of CYP3A4 and GST variant alleles:

Genotypic and allelic frequencies of CYP3A4*18 and GSTP1 were determined for the 4 patients of Family A and compared with 33 healthy controls. The CYP3A4*18 is a variant allele in exon 10 involving thymine (T) to cytosine (C) transition at the position 169068 that changes leucine (Leu) to proline (Pro) at the site 293. Therefore, the three genotypes for CYP3A4*18 are Leu.Leu (wild type: T.T), Leu.Pro (heterozygous mutant: T.C), and Pro.Pro (homozygous mutant: C.C). All our tested patients harbored the T.T wild type. The GSTP1 is a variant allele in exon 5 involving adenosine (A) to guanine (G) transition in the 313 position that causes an isoleucine (Ile) to valine (Val) substitution at the site 105 that leads to decreased enzyme activity. Therefore, the three genotypes for GSTP1 are Ile.Ile (wild type; A.A), Ile.Val (heterozygous mutant; A.G), and Val.Val (homozygous mutant; G.G). Of the 14 tested individuals, 6 were wild type A.A and 8 were heterozygous A.G. Of the 3 affected individuals one was A.A and the two others were A.G.

Sequencing:

Genetic analysis by Sanger sequencing of *FAN1* of the proband of each family allowed us to identify two different mutations in exon 12: In patient IV-2 of family A we found a homozygous frameshift mutation due to a one-basepair deletion (c.2616delA) resulting in the appearance of a premature STOP codon (p.Asp873ThrfsTer17) (Figure 4). This mutation was previously reported in a family with KIN by Zhou et al. [5]. In patient II-3 of family Z we found a homozygous frameshift mutation due to a one-base-pair deletion (c.2603delT) resulting in the appearance of a premature STOP codon (p.Leu868ArgfsTer22) (Figure 4). This mutation was reported neither in the literature nor in online databases as polymorphism. This variant detected in the *FAN1* was not reported previously. In-silico prediction programs classified the mutation as "pathogenic". In fact we assessed the possible functional impact of the new variation (p.Leu868ArgfsTer22) using PolyPhen2, SIFT and Varsome. The three programs showed a consistent

result of the deleterious effect of this mutation. The mutations identified were tested for familial segregation. The variation was found to segregate with the phenotype and in obligate carriers. The parents of the proband of the family Z were heterozygous for the mutation; the rest of the family was not tested.

Discussion

In our study, we confirmed biopsy proven KIN in 2 siblings from family A and one patient from family Z. According to the family clustering of KIN previously described [2, 4, 8], we concluded that it was the same nephropathy in all patients.

KIN is a rare but probably an underdiagnosed condition. Its prevalence is below 1% in patients who had renal biopsy [9].

In our nephrology department, we found 3 cases among 8870 renal biopsy. This underdiagnosed condition is due to several reasons: clinical presentation is not specific, chronic tubulo-interstitial nephritis is usually asymptomatic and kidneys are too small to make biopsy. The biggest series is that of Bhandari et al. [8] (6 cases) followed by Spoendlin et al. [4] (4 cases). The review of the available literature reveals approximately 33 reported cases until now. In Tunisia, 3 cases were reported by Hassen et al. [3].

In this paper we report 6 additional cases of KIN with histological evidence in 3 patients. In our series of patients, the mean age at first documentation of nephropathy was 26.83 years. In the literature, the average age is 36.42 years. Indeed, most patients including ours developed a progressive renal failure beginning in the third decade of life. The evolution to ESRD is usually at an age of 37.22 years (36.5 years in our series).

Patients had a history of recurrent infections mainly involving the respiratory tract, which was not noted in our series. Transient elevations of liver enzymes were found in our patients as described in others [2, 9, 10].

KIN is a chronic tubule-interstitial disease that was first described in two siblings and in an unrelated third patient with progressive chronic renal failure [2]. The kidney showed bizarre karyomegaly and nuclear polymorphism predominantly of tubular cells and interstitial fibrosis accompanying tubular atrophy. We describe here 3 additional cases with slowly progressive renal failure and the same histological characteristic findings.

Karyomegaly is not limited to the kidneys. In patient reported by Mihatsch [2], biopsy specimens of several organs and the autopsy of one patient disclosed polymorphic enlarged nuclei in epithelial and mesenchymal cells of the kidneys and many other organs, i.e. smooth muscle cells of the intestine, alveolar epithelial cells, brain astrocytes, bile duct epithelium and Kupffer cells. In our cases, one liver biopsy was performed and did not show karyomegalic cell nuclei.

KIN has been long described as a nephropathy of unknown etiology and pathogenesis. Karyomegalic changes in renal cells have been reported in different pathologic settings, both in human and experimental animals, including heavy metals toxicity [11, 12, 13] and virus infection (CMV).

In addition and because of the similarity of KIN with Balkan nephropathy [14, 15, 16, 17] other potential etiologies including OTA have been convincingly included by other investigators. Burry's [18] and Sclare's cases [19] were reported as affected by KIN and were found to have OTA in their blood and urine, a mycotoxin produced by a number of aspergillum and penicillium species which has been shown to cause karyomegalic lesions in proximal tubuli in rats [20, 21, 22]. The most important toxic effect of this mycotoxin is nephrotoxicity.

Studies in Tunisia, Algeria, Morocco and Egypt have shown similar disease symptoms with high incidence of chronic interstitial nephropathies of unknown etiology. Hassen et al. confirmed the involvement of this nephrotoxic mycotoxin present at high blood levels in Tunisian population in the outcome of tubulo-interstitial nephritis with unknown etiology [23, 24].

OTA is a possible, but not the only, etiologic factor in triggering KIN. In fact KIN seems to be rather multifactorial involving especially a genetic predisposition. Family clustering, highest frequency of the haplotypes HLA A9 B35 and different susceptibility to develop the nephropathy in spite of a high OTA contamination in all subjects support a genetic etiology. Besides, family clustering was reported more than once [2, 3, 4, 8, 9, 10, 25, 26, 27].

We first studied polymorphisms CYP3A4*18 and A313G respectively for the genes CYP3A4 and GSTP1 in the family A because these genes are involved in the metabolism of the OTA [28].

However, the frequency of these polymorphisms differs according to the ethnic group: 20.3% in the Chinese population [29] against 2% in the Tunisian population [30] for CYP3A4*18 and 30% for the Caucasian population [27] against 1% for the Tunisian population [30] for A313G. These low frequencies in the Tunisian population could explain the absence of significant association between polymorphisms CYP3A4*18, A313G and KIN in family A. The only study made on the Tunisian population [30] did not either find association between these polymorphisms and the arisen of a renal disease including the KIN, so confirming our results.

Recently Zhou et al [5] identified recessive mutations of *FAN1* as causing KIN, which leads to CKD with fibrotic degeneration of the kidney. They performed homozygosity mapping and whole exome sequencing (WES) in two siblings of Maori descent in order to identify additional causative genes for Nephronophthisis (NPHP)-related ciliopathies, a heterogeneous group of recessive diseases that cause CKD [31].

They obtained by homozygosity mapping 7 candidate regions of homozygosity by descent and identified by WES a homozygous nonsense mutation (Trp707*) in *FAN1* in both affected siblings. This truncating mutation was the only homozygous variant detected within the mapped candidate regions. They also

performed Sanger sequencing of all *FAN1* exons in 5 published KIN families and 5 unpublished cases, and identified 12 different mutations in 9/10 families with KIN. Eight of the 12 mutations truncated the conceptual reading frame. They concluded that these recessive mutations of *FAN1* are the cause of KIN for these families. By taking into account these results, we sequenced *FAN1* for the affected members of our families. Sequencing allowed us to identify 2 different mutations for each family.

A homozygous frameshift mutation due to a one-base-pair deletion (c.2616delA) resulting in a premature STOP codon (p.Asp873ThrfsTer17) was detected in family A (Figure 4). This variant was previously reported by Zhou et al. [5]. A homozygous frameshift mutation due to a one-base-pair deletion (c.2603delT) resulting in a premature STOP codon (p.Leu868ArgfsTer22) was detected in family Z (Figure 4). Three frameshift mutations in the exon 12 of *FAN1* were reported in the literature in families with KIN [5], our mutations are the newest ones.

FAN1 encodes Fanconi anemia-associated nuclease 1. *FAN1* mutations cause karyomegalic interstitial nephritis, linking chronic kidney failure to defective DNA damage repair [5], an endonuclease that interacts with FANCD2 and FANCI on Interstrand DNA crosslinks (ICL)- induced DNA damage response (DDR) and is recruited to the sites of ICL lesions, where its function is critical for resolving ICLs [32, 33, 34, 35].

In fact, failure to remove ICLs can induce cell cycle arrest, cell death and genome instability. However recent studies showed that deficient cells in both FAN1 and components of the FA pathway are more sensitive to ICL-inducing agents than the respective single mutants, suggesting that in ICL repair the role of FAN1 is not the same as the one in the FA pathway [36].

These findings suggest that biallelic mutations in *FAN1* cause KIN [5] instead of FA. The cause of the karyomegaly in KIN is not yet understood, and it is not clear whether it or any other characteristics of KIN in patients with *FAN1* mutations is caused by defective ICL repair.

Furthermore, it is not clear whether the nuclease activity of FAN1 is required to prevent KIN. The basis of a functional difference between FAN1 and the FA pathway in ICL repair will be an important area of investigation. It is possible that FAN1 may respond to a subset of ICLs that is somehow different in nature from the ICLs dealt with by the FA pathway. This might reflect a difference in the chemical nature of the ICLs or a difference in the genomic context of the ICLs recognized by the two pathways [37].

Like ours, other studies reported homozygous mutations in *FAN1* associated with detectable OTA in urine and blood samples [25]. *FAN1* mutations could result in more sensitive tubular cells to environmental genotoxin like OTA inducing renal DNA damage. Another study [38] on the identification of mutations in 2 other genes ZNF423 and CEP164 in patients with renal ciliopathies, confirmed the presence of a link between the pathogenesis of chronic kidney diseases and defective DNA damage repair.

More recently, Law et al [39] report the first case of concurrent LECT2 amyloidosis and KIN combined with a novel deletion in the *FAN1* gene. These two rare causes of chronic kidney disease have been described

in the same patient for the first time, which highlights the importance of renal biopsy in chronic kidney disease of unclear aetiology.

In conclusion, our study is the first Tunisian report of familial cases of KIN with mutations involving the *FAN1* gene, which plays a key role in DNA repair. These mutations are not sufficient to develop KIN, in fact additional environmental factors, such as OTA, with inadequate DNA repair are hypothesized to cause the disease.

Declarations

Ethics approval and consent to participate

All procedures performed in the present study were approved by The Ethical Review Committee of Mongi Slim Hospital (La Marsa, Tunisia) and were also in accordance with the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study.

Consent for publication

Consent was obtained from all individual participants included in the study.

Availability of data and materials

The authors declare that all relevant data are included in the article, and that it is also available from the corresponding author by request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

IR contributed to sample collection, analyzed clinical data, performed Sanger sequencing and segregation analysis, and drafted the paper; MJ and HG contributed to collection of clinical data; HJ, YE and SH contributed to genetic counseling; RA, HH and TB analyzed the renal biopsies; CZ, SA and HA performed the laboratory investigations, LB and RG designed and initiated the study, monitored data collection and analysis for the study and revised the paper.

All authors read and approved the final manuscript.

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Figures

Figure 1

A: Pedigree of the family A, B: Pedigree of the family Z

Figure 2

Renal histology in Patient IV-7 and Patient IV-12 in family A A: Renal biopsy. Masson's trichroma (magnification $\times 400$) Proximal tubules with giant nuclei, irregular nuclear membrane (Patient IV-7) B: Renal biopsy, hematoxylin and eosine stain (magnification $\times 200$) giant nuclei with irregular nuclear membrane (Patient IV-7) C and D: Renal biopsy, electron microscopy: giant Karyomegalic nuclei with irregular nuclear membrane (Patient IV-7) E: Renal histology in individual IV-12: Renal biopsy, electron microscopy: giant Karyomegalic nuclei of epithelial cells of proximal tubules.

Figure 3

Renal histology in Patient II 3 in family Z A: Renal biopsy. Masson's trichroma (magnification ×200): giant nuclei of tubular epithelium B: Renal biopsy. Masson's trichroma (magnification ×400): giant nuclei of tubular epithelium, moderately inflammatory interstitial fibrosis C: Renal biopsy. Hematoxylin and eosine stain (magnification ×200): karyomegalic nephropathy D: Renal biopsy. Masson's trichroma (magnification ×400): normal glomerulus

Figure 4

I: Electropherogram showing the mutation c.2616delA found in family A (A and C: mutation found in patient IV-2, B and D: wildtype II: Electropherogram showing the mutation c.2603delT found in family Z (A and C: wildtype, B and D: mutation found in patient II-3)