ONOMY Science

American journal of Nephrology & Therapeutics
ISSN 2643-7007

Case report Open Access

# Genetic Heterogeneity in a Multigenerational West Virginia Family for Periodic Fever Syndrome

**Abdullah Shabarek[1], MD, Amee Amin[1], MD, Rose Ayoob[2], MD, Myra Chiang[2], MD**

[1.] Department of Pediatrics, Charleston Area Medical Center/West Virginia University, 830 Pennsylvania Avenue, Suite 104, Charleston, WV 25302, USA, WV

[2.] Department of Pediatrics, Section of Nephrology, Charleston Division, West Virginia University, 830 Pennsylvania Avenue, Suite 104, Charleston, WV 25302, USA, WV

***Corresponding Author: Myra Chiang,** Department of Pediatrics, Section of Nephrology, Charleston Division, West Virginia University, 830 Pennsylvania Avenue, Suite 104, Charleston, WV 25302, USA; Email: mlchiang@hsc.wvu.edu

**Citation:** Genetic Heterogeneity in a Multigenerational West Virginia Family for Periodic Fever Syndrome; Am J of Nep and Ther. 2021; 4(1): 01-09.

**Submitted:** 31 May 2021; **Approved:** 08 June 2021; **Published:** 10 June 2021

## Abstract

Periodic Fever Syndromes are a group of autoinflammatory disorders that are caused by abnormal activation of innate immunity arising from inheritable gene mutations. Two common syndromes are Familial Mediterranean Fever (FMF) and Tumor Necrosis Factor Receptors Associated Periodic Syndrome (TRAPS), which are characterized by periodic, recurrent episodes of fever and systemic symptoms such as abdominal pain, arthralgia, skin rash, myalgia, periorbital edema and lymphadenopathy. Both disorders can lead to renal and hepatic amyloid accumulation.

We describe a multigenerational family in West Virginia that presented with renal amyloidosis and an initial diagnosis of autosomal dominant FMF (ADFMF). All affected family members died from kidney failure at an early age. Wider availability of genetic testing later indicated that this family may have suffered from Tumor Necrosis Factor Receptors Associated Periodic Syndrome (TRAPS) which presents very similarly clinically and is also inherited as autosomal dominant. Both disorders result in uncontrolled production of interleukin-1, leading to recurrent episodes of inflammation, and an excess production of amyloid A protein with subsequent deposition in the kidneys, and other organs, including the liver. Both disorders have variable expression, and the prognosis depends on the degree of penetrance. Colchicine had been the main treatment of FMF, however, targeted therapy (anti-IL1 beta) is the treatment of choice for TRAPS. In some patients, both therapies may be necessary, especially if renal amyloidosis is already present.

This report underscores the importance of early diagnosis, and genetic testing as targeted therapy may be available and may lead to a better outcome.

**Keywords:** Periodic fever syndromes, tumor necrosis factor receptors associated periodic syndrome (TRAPS), familial Mediterranean fever (FMF), renal amyloidosis.

## Abbreviations:

AA: Secondary Amyloidosis
ANA: Antinuclear antibody
Anti DS-DNA: Anti Double Stranded Deoxyribonucleic Acid
Anti ENA: Anti Extractable nuclear antigens
Anti GBM: Anti Glomerular Basement Membrane
ARFMF: Autosomal Recessive Familial Mediterranean fever
C-ANCA: Antineutrophil Cytoplasmic Antibodies
CCHMC: Cincinnati Children's Hospital Medical Center
CRP: C-reactive Protein
ESR: Erythrocyte Sedimentation Rate

***Cite this article:*** Genetic Heterogeneity in a Multigenerational West Virginia Family for Periodic Fever Syndrome; Am J of Nep and Ther. 2021; 4(1): 01-09.

FDA: Food and Drug Administration
FHF: Familial Hibernian Fever
FMF: Familial Mediterranean Fever
GFR: Glomerular Filtration Rate
HDS: Hyperimmunoglobulinemia D syndrome
IL-1: Interleukin 1
JO-1: Anti synthetase antibody
SSB La: Sjogren's Syndrome antibodies
SSB Ro: Sjogren's Syndrome antibodies
PCP: Primary Care Provider
RF: Rheumatoid Factor
RNP: Anti Ribonucleic Protein antibodies
SM: Anti smith antibodies
TRAPS: Tumor Necrosis Factor Receptors Associated Periodic Syndrome
T4: Thyroxin
TSH: Thyroid Stimulating Hormone

## Introduction

Periodic fever syndromes, also called autoinflammatory diseases, describe a group of rare diseases characterized by inappropriate antigen-independent hyperactivation of the immune system leading to inflammation and tissue injury. By far, the most common is ARFMF. Though it is most common in individuals of Mediterranean descent, FMF has also been reported at a lower prevalence in several other populations including Asians. Depending on the ethnic background, the prevalence can be as high as 1:500 in Armenians to 1:73,000 in Ashkenazi Jews (1). The prevalence in US is reported to be 1:40,000. Males and females are affected equally. On rare occasions, FMF can be inherited as autosomal dominant. In 1997, the gene (FEMV) causing ARFMF was identified by positional cloning and was mapped to the short arm of chromosome 16. This gene codes for the protein known as pyrin, also called marenostrin. More than 310 sequence variants in the MEFV gene have been identified, but only few are associated with a disease phenotype (2). Uninhibited pyrin activity results in uncontrolled release of interleukin-1 (IL-l), leading to episodes of inflammation. The recurrent episodes of inflammation are presumed to lead to excess production of amyloid A protein with subsequent deposition in organs. Disease onset is typically during childhood, however, delay in diagnosis is common, especially in non-Mediterranean individuals. Classic ARFMF is characterized by a self-limiting, short (2-4 days) episode of fever. Other manifestations include abdominal pain from non-infectious peritonitis, chest pain from pleuritis, joint pain commonly of the knees, ankles and wrists from arthritis/synovitis, myalgia and erysipelas like skin rash. Leukocytosis and elevated levels of acute-phase reactants such as ESR, CRP, fibrinogen are frequently observed during disease flares. As the attack abates, the elevated levels return to normal range. In the interim, patients may be totally asymptomatic. Even among members of a family, the severity, duration, frequency, and trigger of attacks are variable. Intercurrent infections, emotional stress, vigorous exercise, surgery and menstruation are some of the reported triggers. Progressive amyloid deposition is the major cause of mortality. It commonly affects the kidneys, but deposition can also occur in the liver, spleen, gastrointestinal tract, thyroid glands, heart. Secondary (AA) amyloidosis in the kidneys can present initially as asymptomatic proteinuria or frank nephrotic syndrome. It is estimated that without treatment, end-stage kidney disease develops 2 to 13 years after the onset of proteinuria (2). The prevalence of amyloidosis varies depending upon the specific mutation of the MEFV gene. Some individuals develop amyloidosis without the classic symptoms associated with FMF. These cases are referred to as FMF type 2. The introduction of colchicine in 1972 as a prophylactic treatment in FMF has dramatically reduced the frequency of attacks and if introduced early can forestall the development of amyloidosis. Colchicine

***Cite this article:*** Genetic Heterogeneity in a Multigenerational West Virginia Family for Periodic Fever Syndrome; Am J of Nep and Ther. 2021; 4(1): 01-09.

reduces inflammation by inhibiting leukocyte migration. It requires strict daily adherence. In patients with inadequate response to colchicine, adding agents directed towards IL-1 may be effective. In 2016, canakinumab (Ilaris) was approved by the US Food and Drug Administration (FDA) as treatment for FMF.

Autosomal dominant form of FMF had been rarely described. Unlike the recessive form, this primarily affects persons of European extraction (3). The attacks are much longer in duration, lasting two to four weeks in most patients but the frequency of recurrence is lower, averaging less than 2 per year (4). The response to colchicine is not as good compared to the recessive form and requires a higher dose (5).

Although TRAPS is thought to be the next most common autoinflammatory disease, compared to ARFMF, it is relatively rare with a prevalence of 1:1,000,000. It was first described in 1982 as Familial Hibernian Fever because the first cases reported were in patients with Irish/Scottish background, but the disease has since been seen in other ethnic groups. It was renamed as TRAPS in 1999 after McDermott defined a family of dominantly inherited autoinflammatory syndrome due to mutations in the extracellular domains of the 55 kDa tumor necrosis factor receptor superfamily member 1A (TNFRSF1A) gene on chromosome 12 (6). Most TNFRSF1A gene mutations result in a TNFR1 protein that is folded into an incorrect shape which are trapped within the cell and are not able to go to the cell surface to interact with TNF. These protein clumps inside the cells are thought to trigger other pathways involved in causing inflammation (7). Although TRAPS is inherited as autosomal dominant, there is genetic heterogeneity and variable penetrance. Mutations affecting cysteine residues and the T50M variant have been widely regarded as associated with higher penetrance, a more severe disease phenotype and high risk for development of amyloidosis, whereas the R92Q variant is usually associated with a milder disease without amyloidosis (7). TRAPS affects males and females equally. Classic TRAPS presents with recurrent fever that typically lasts around three weeks but can vary from a few days to a few months. The frequency of attack is variable even within the same family, ranging from every month to every few years or longer. These episodes most often begin in childhood but may begin at any age. Disease flares can occur spontaneously or following a variety of triggers similar to FMF. Additional findings during episodes of fever include abdominal pain, myalgia, arthralgia, gastrointestinal symptoms, skin rash and lymphadenopathy. The presence of periorbital edema was once thought to be pathognomonic but is only seen in 20% (7). Acute phase reactants are elevated during the attack. About 25% develop amyloidosis which can lead to kidney or liver failure. The presence of proteinuria or nephrotic syndrome suggests renal amyloidosis. Due to reduced penetrance, some individuals who inherit the mutated gene may never develop features of TRAPS (8). Just like FMF, prognosis depends largely on the development of amyloidosis. In September 2016, the US FDA approved IL-1 antagonist canakinumab (Ilaris) as first line treatment for TRAPS, administered as a 2mg/kg monthly subcutaneous injection.

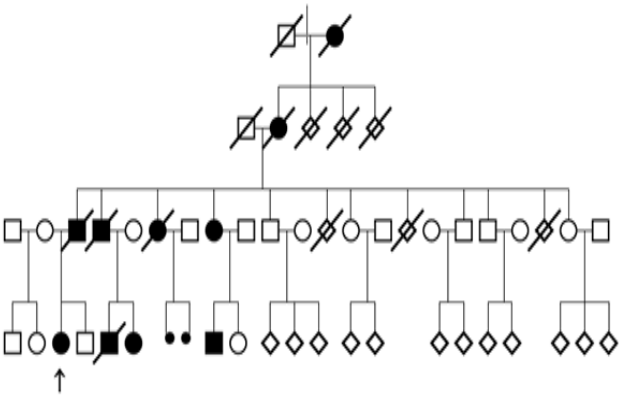
## Case reports

### Case 1

A 13-year-old female was admitted to our facility in 1997 with a history of recurrent episodes of spiking fevers, abdominal pain, joint pain of the lower extremities, and a transient migratory skin rash. The symptom complex had been active for approximately two weeks and was increasing in severity over time. The abdominal pain was described as diffuse and crampy accompanied by frequent loose stools. Severe joint pain in the lower extremities resulted in the inability to bear weight at times. She described her skin rash as red, tender, which would spontaneously appear and resolve within a relatively short period of time. These episodes began at 3 years of life with recurrences of variable severity and at least four previous hospitalizations during severe attacks. She was diagnosed with juvenile idiopathic arthritis during one of these admissions. Milder episodes occurred one or two times per year, precipitated by strenuous physical activity. Fevers and skin rash were an occasional feature. Family history was significant for FMF in four consecutive generations in this family of German ancestry (Fig. 1).

***Cite this article:*** Genetic Heterogeneity in a Multigenerational West Virginia Family for Periodic Fever Syndrome; Am J of Nep and Ther. 2021; 4(1): 01-09.

**Fig1: Autosomal Dominant Familial Mediterranean Fever-like Syndrome in a West Virginia Kindred**



Three of the persons affected with FMF had died in early adulthood as a consequence of renal failure secondary to amyloid nephropathy. A fourth affected person had committed suicide at age nineteen due to recurrent unbearable pain. There was no family history of autoimmune disease, connective tissue disorders, primary amyloidosis or primary kidney disease. At the time of her presentation, she appeared acutely ill and in moderate distress. Her temperature was 40.6 C. Her weight was at the 20th percentile, height was in the 50th percentile. Pertinent negative findings included a normal HEENT exam with absence of periorbital edema, conjunctival injection or lymphadenopathy. There was mild tachycardia. Diffuse abdominal tenderness with voluntary guarding was present, however, rigidity or rebound tenderness was not elicited. An erysipelas-like skin rash was present on the anterior thorax and ankles. The skin lesions were exquisitely tender to palpation. There was pain with both passive and active motion of the joints of the lower extremities, but no joint swelling or focal tenderness. Initial laboratory findings included 500 mg/dl protein on urinalysis. Urine protein to creatinine ratio was 6.9 (nephrotic range). There was marked leukocytosis with WBC count of 31.9, 68% neutrophils, 29% bands. Hemoglobin and hematocrit were 12.2 gm/dl and 35.7%, platelet count was 468,000. BUN was 19 mg/dl, creatinine 1.5 mg/dl, total protein 6.8 mg/dl, albumin was 2.3 mg/dl. Antinuclear antibody (ANA) and rheumatoid factor (RF) were negative. Serum C3, C4 complements and IgD level were within normal limits. Free T4 was normal however TSH was moderately elevated at 8.5 mIU/ml. Thyroid antibodies were negative. Acute phase reactants were all elevated with ESR of 138 mm/hr, CRP of 192 mg/L, fibrinogen of >900 mg/dl, haptoglobin of 632 mg/dl. Abdominal series and chest x-ray were unremarkable. Renal ultrasound demonstrated mild prominence of the right renal pelvis but was otherwise unremarkable. Renal biopsy revealed amyloidosis with moderate glomerular and interstitial damage. Amyloid deposits were found in the mesangium, capillary loops of glomeruli, blood vessels, and in the interstitium (Fig. 2A-D).

**Fig2A: Glomerulus with amyloid deposits, H&E stain**

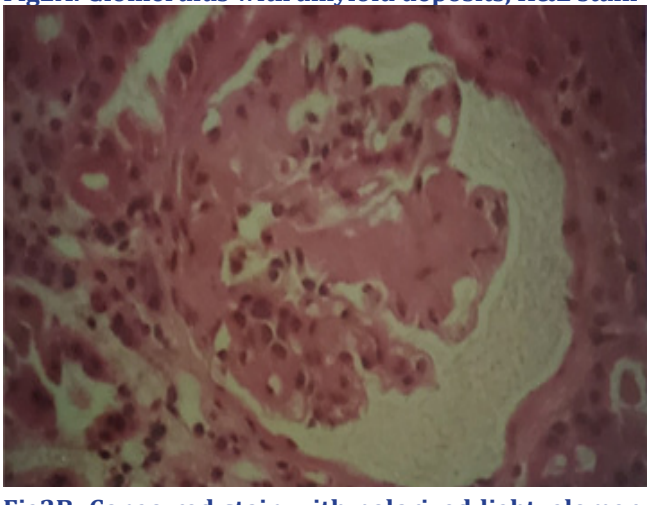


**Fig2B: Congo red stain with polarized light, glomerulus**

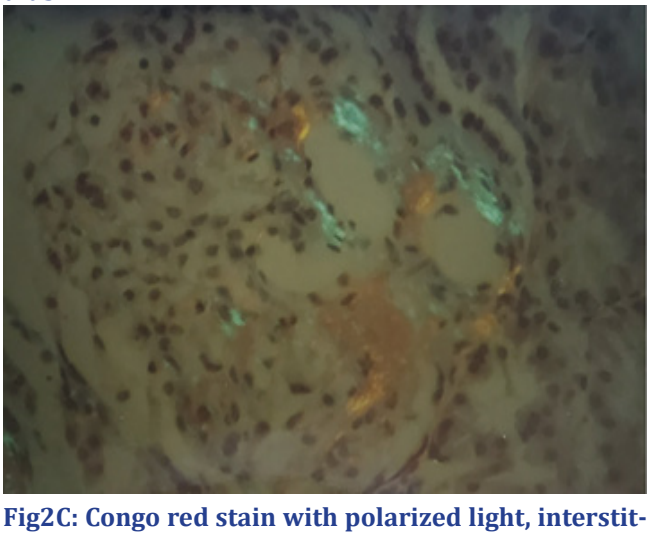


**Fig2C: Congo red stain with polarized light, interstitium**

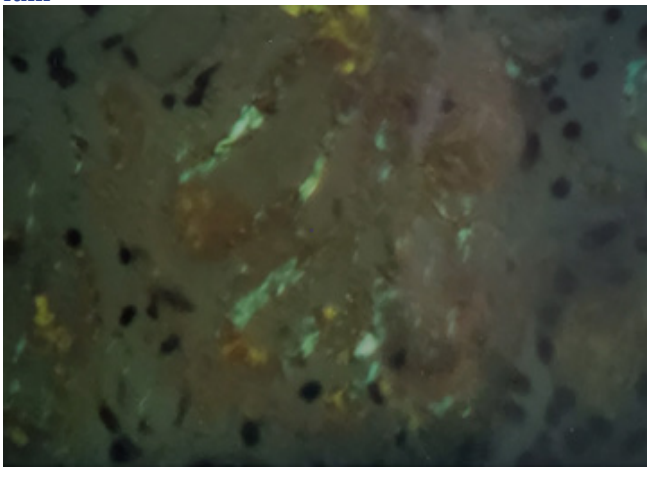
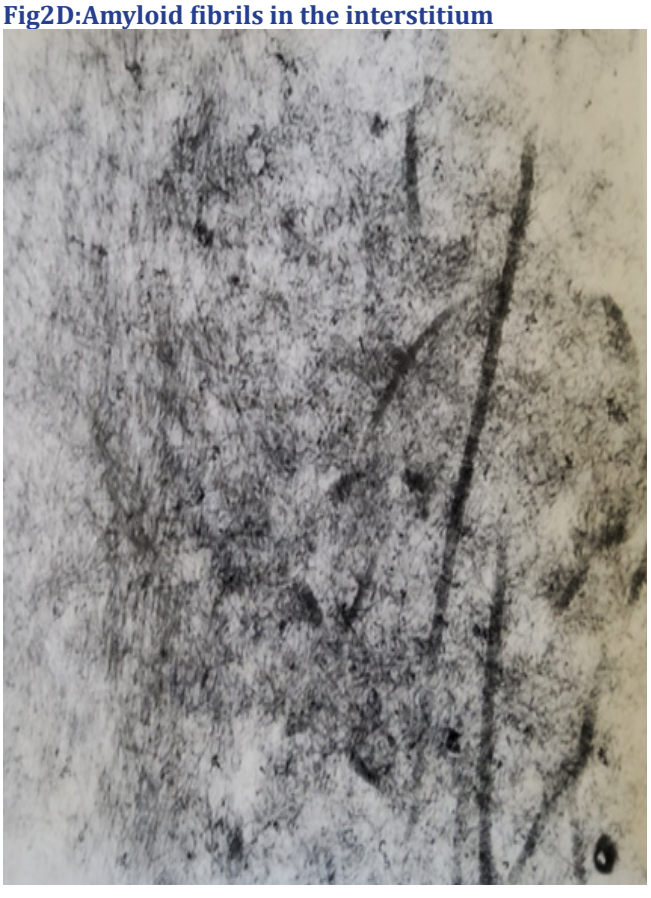


**Fig2D:Amyloid fibrils in the interstitium**



Immunofluorescent studies found no evidence of IgA, IgG, IgM, C3, fibrinogen or light chain proteins. Genomic DNA was sequenced using dye terminator chemistry, and results were compared to the published Genbank sequence for ARFMF. The analysis failed to show mutation at the sites known to be responsible for ARFMF. Based on this finding and the family pedigree, the patient was diagnosed with AD-FMF. Other differential diagnoses considered at that time were Hyperimmunoglobulinemia D syndrome (HIDS), this was ruled out as her serum IgD level was normal and amyloidosis is rare in HIDS. We also considered Familial Hibernian fever (FHF), however, the absence of two of the most characteristic symptoms of periorbital edema or red stinging eyes, and non-Irish descent made this diagnosis less likely.

The patient was started on colchicine 0.6 mg TID. Approximately nine months after starting colchicine, she experienced only one recurrence of her disease. Her urinalysis was normal, and her urine protein creatinine ratio was down to 0.08. Her serum creatinine improved to 0.9 mg/dl. Serum albumin went up to 3.2 mg/dl. Her TSH level came down to 2.7 mIU/L. Renal biopsy was repeated two years after diagnosis. This demonstrated a moderate improvement of amyloidosis with decreased interstitial deposition of amyloid fibrils. Unfortunately, adherence with daily colchicine was not maintained and after experiencing initial improvement, proteinuria became worse and her renal function progressively declined. During this time, she had several severe disease flares requiring hospital admissions for vomiting, dehydration and acute kidney injury, along with conjunctivitis and periorbital edema at times. A third kidney biopsy demonstrated that >70% of her glomeruli were fibrotic. Three years after diagnosis at age 16, she was started on home peritoneal dialysis (CCPD). She got married when she was 17- years old. Due to non-adherence with medications, office visits and dialysis, kidney transplantation was initially put on hold. Two years after starting dialysis, she received a deceased donor renal transplant. She delivered two boys by cesarean section in 2007 and 2010, at age 23 and 26 years respectively. Ten years after her transplant, she lost her kidney and went back on dialysis. She suffered from major depressive disorder, and at the age of 31, she passed away from liver failure secondary to liver amyloidosis.

## Case 2

10-year old son of case 1 was found to have persistent proteinuria on two occasions during routine office visits. He was referred to our clinic and was seen four months after a urine dipstick at his primary care provider (PCP) demonstrated proteinuria. His medical history was unremarkable aside from chronic constipation for which he was taking Miralax (polyethylene glycol 3350). Father denied any history of recurrent episodes of fever, abdominal pain, chest pain, joint pain, skin rash. His father mentioned to his medical providers that his deceased wife had FMF, had a kidney transplant and died from liver failure. Except for an elevated BP of 129/90mmHg, his physical exam was unremarkable. Weight and height were around the 5th percentile. There was no edema. His urine dipstick demonstrated >300 mg/dl protein, urine protein creatinine ratio was 6.4 (nephrotic range). BUN was 16mg/dl, creatinine 0.4mg/dl, serum albumin 2.8mg/dl, freeT4 was normal but TSH was elevated at 6.4mIU/L. A week later, he was seen in a local clinic for fever, vomiting and sore throat and was diagnosed with group A strep pharyngitis

and was started on amoxicillin, and ibuprofen for fever. Four days later, his father noticed periorbital edema. Due to persistent fever and eye swelling, he was evaluated by his PCP who ordered blood test that showed leukocytosis, elevated BUN of 55mg/dl, creatinine of 4.1mg/dl. Due to concerns for acute kidney injury, he was transferred to Cincinnati Children Hospital Medical Center (CCHMC) for admission. On arrival, he was noted to be well appearing without obvious edema. Initial labs were remarkable for leukocytosis, elevated inflammatory markers (ESR of 116mm/hr, CRP of 7.4mg/L, fibrinogen of 737mg/dl). Urine protein creatinine ratio of 31.74, with no hematuria. BUN was 68mg/dl, creatinine 4.12mg/dl, serum albumin 1.1mg/dl. Pediatric nephrology was consulted. Acute post streptococcal glomerulonephritis was ruled out based on absence of hematuria. ASO titer was elevated at 1580, but C3, C4 complement levels were normal. Other tests included ANA, anti-DS DNA, C-ANCA, anti-ENA, anti-GBM which were all negative. Renal ultrasound showed enlarged and echogenic kidneys. Liver ultrasound demonstrated increased echogenicity of the liver. Kidney biopsy demonstrated significant amyloid deposition in glomeruli and small blood vessels. There were additional findings suggestive of acute tubular necrosis and acute interstitial nephritis with patchy eosinophilia (Fig. 3A-E).

**Fig3A: The mesangium are tremendously expanded by amorphous eosinophilic acellular material. The same amorphous material is present in the walls of small arteries and arterioles, H&E stain**

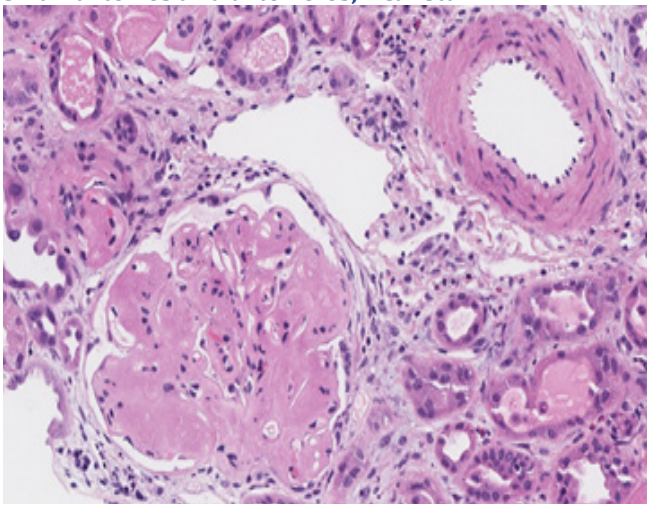


**Fig3B: The proteinaceous deposition in the glomeruli is accompanied by an interstitial inflammation which includes numerous eosinophils, H&E stain**

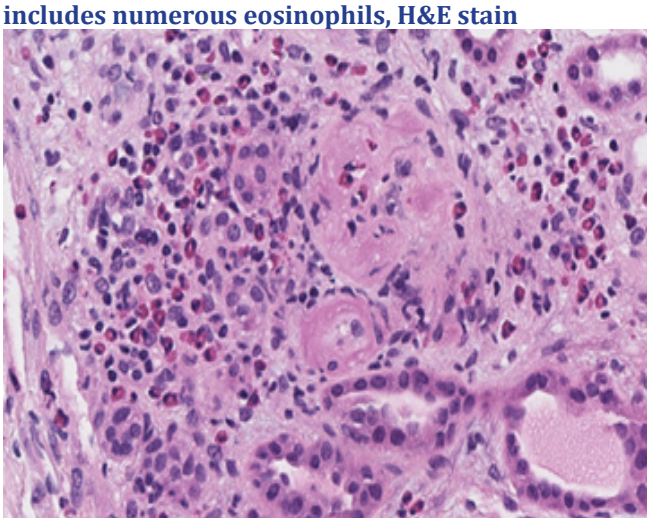


**Fig3C: The protein deposition in the glomeruli is accompanied by significant tubule injury, consistent with a component of acute tubular necrosis, H&E stain**

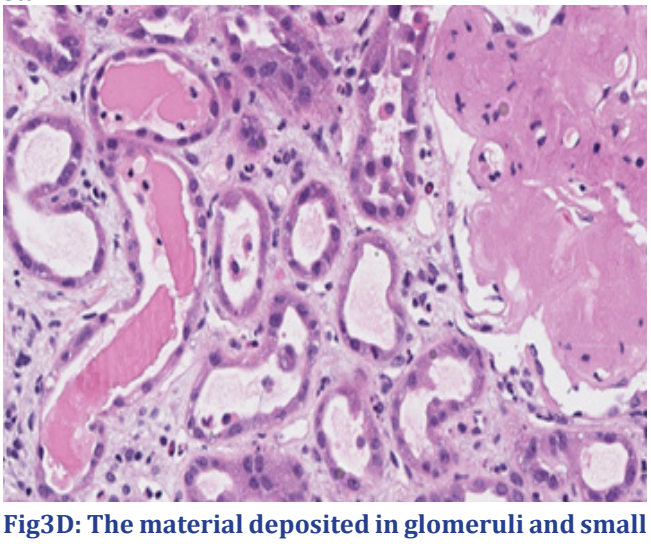


**Fig3D: The material deposited in glomeruli and small arteries/arterioles is brightly Congophilic (bright red on this stain) with the expected green birefringence on polarization**

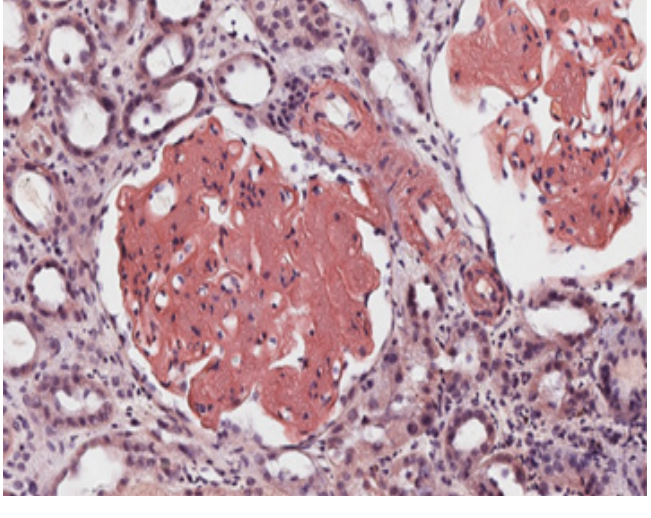
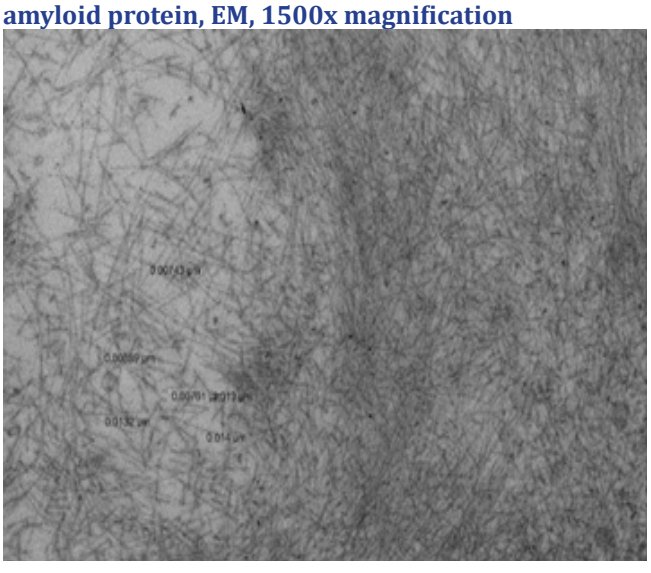


**Fig3E: On very high magnification, the amorphous material is identified as haphazardly arranged fibrils, 8-13 nanometers in diameter, consistent with amyloid protein, EM, 1500x magnification**



Genetics and Pediatric rheumatology were later consulted. Additional lab work (IgA, IgG, IgM, JO-1 antibody, LA (SSB), RO (SSA), RNP, SM) ruled out other rheumatologic conditions. Genetic testing for Periodic Fever Syndrome panel was sent to Invitae. Based on the clinical presentation, family history and renal biopsy result, he was given a provisional diagnosis of FMF Type 2. Colchicine was started along with IV pulse steroid daily for three doses for treatment of acute interstitial nephritis. He developed hypertension and was started on amlodipine. After six days, he was discharged home on oral prednisone 30 mg daily, colchicine 0.3 mg daily (dose adjusted for low GFR), amlodipine 5 mg daily and furosemide 40 mg BID.

Three days after hospital discharge, he was admitted to Charleston Area Medical Center due to worsening edema requiring several rounds of 25% albumin and diuretics IV. He was discharged home after three days with improved edema. His genetic test came back positive for pathogenic c.175T>C (p.Cys59Arg) variant of TNFRSF1, giving a diagnosis of TRAPS. He was started on monthly 150 mg subcutaneous injection of canakinumab. The patient continues to follow with nephrology and rheumatology at CCHMC. He came off oral steroid after five months. Due to extensive amyloid deposits in the kidneys, decision was made to continue both colchicine and canakinumab. He remains hypertensive requiring two medications. His serum creatinine stabilized at 0.5-0.6 mg/dl but his cystatin c off steroid was elevated at 1.35, giving a calculated GFR of 65 ml/min. His repeat liver ultrasound was normal. Because of persistent elevation of TSH, he was started on levothyroxine by Endocrine. The patient continues to have no symptoms of fever, abdominal pain, joint pain, skin rash, myalgia. There's been no recurrence of periorbital edema. His energy is excellent. At his last visit (nine months after initiation of canakinumab), his urine protein creatinine ratio was down to 0.86. ESR was 17mm/hr, CRP <0.4mg/L. Serum albumin was 3.7mg/dl, liver enzymes were normal. However, his serum creatinine went up to 0.85mg/dl, cystatin c went up to 1.87 with calculated GFR of 47 ml/min. Plan is to repeat kidney biopsy.

## Case 3

This is the older brother of case 2. He has the same genetic mutation as his brother but at the age of 12, he is asymptomatic, has normal blood pressure, urinalysis, renal function, ESR and CRP.

## Discussion

In this report, we describe a two generation (mother and two sons) family with Periodic Fever Syndrome with varying presentations. The mother exhibited symptoms suggestive of FMF at age three but was not diagnosed until age 13, by which point there was extensive amyloid deposits in the kidneys. Based on her ethnic background, clinical presentation and family history, she was diagnosed with autosomal dominant form of FMF. Genetic testing at the time of her diagnosis was not available. Like her predecessors, she died at a young age of 31 secondary to amyloidosis. Her 10-year-old son never had the classic presentation of FMF or TRAPS, but was found to have extensive amyloid deposits in the kidneys after he presented with nephrotic range proteinuria. He had one episode of periorbital edema which is characteristic of Familial Hibernian Fever (now called TRAPS). His genetic test confirmed the diagnosis of TRAPS. His older brother who has the same mutation is currently totally asymptomatic and has no proteinuria.

In hindsight, the mother likely suffered from the same genetic mutation as her two sons. This underlines the importance of genetic testing for accurate diagnosis, especially since targeted therapy may be available.

A Periodic Fever Syndromes Panel is available at Invitae which analyzes 12 genes that are associated with periodic fevers (Fig. 4).

**Figure 4: Invitae Periodic Fever Syndromes Panel**

| Gene | Disorder | Protein name | Protein symbol |
|---|---|---|---|
| ADA2 | ADA2 deficiency | cat eye syndrome chromosome region, candidate 1 | CECR1 |
| ELANE | Elastase deficiency (SCN1), cyclic neutropenia | elastase | ELANE |
| LPIN2 | Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome) | lipin 2 | LIPIN2 |
| MEFV | Familial Mediterranean Fever | pyrin | PYRIN |
| MVK* | Mevalonate kinase deficiency | mevalonate kinase | MVK |
| NLRC4 | NLRC4-MAS (macrophage activation syndrome), Familial cold autoinflammatory syndrome 4 | NLR family, CARD containing 4 | NLRC4 |
| NLRP12 | Familial cold autoinflammatory syndrome 2 | NACHT domain-, leucine-rich repeat-, and PYD-containing protein 12 | NALP12 |
| NLRP3 | Muckle-Wells syndrome, Familial cold autoinflammatory syndrome 1, Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA) | cryopyrin | cryopyrin |
| PSMB8 | CANDLE (chronic atypical neutrophilic dermatitis with lipodystrophy) | proteasome subunit, beta-type 8 | PSMB8 |
| PSTPIP1 | Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome | CD2 antigen-binding protein 1 | C2BP1 |
| TNFRSF1A | TNF receptor-associated periodic syndrome (TRAPS) | tumor necrosis factor receptor 1 | TNFR1 |
| TRNT1 | TRNT1 deficiency | tRNA nucleotidyltransferase, CCA-adding 1 | TRNT1 |

As demonstrated in this family, the same genetic mutation can have variable phenotype expression. Absence of classic symptoms can be challenging for monitoring of disease progression or response to treatment. Utilization of elevated inflammatory markers may not be beneficial as these may be normal despite the presence of amyloid deposits. Measurement of serum amyloid A level is currently not available in the US. At present, the only way to assess amyloid deposits in the kidneys is by repeated kidney biopsies which is invasive. We know that amyloid deposits in the kidney precede clinical presentation of proteinuria. This poses the question of do all individuals with a genetic mutation consistent with TRAPS require a kidney biopsy when they are still asymptomatic and have no proteinuria so therapy can be preemptively started?

**Conflict of Interest Disclosure:** The authors have indicated they have no conflicts of interest relevant to this article to disclose.

**Acknowledgement** to Lovell, Daniel, MD, pediatric rheumatology, Mitsnefes, Mark MD and Erkan, Elif, MD, pediatric nephrology, Cincinnati Children's Hospital and Medical Center

**Contributors' Statement Page.**

Dr. Chiang and Dr. Ayoob conceptualized and designed the study, drafted the initial manuscript, and critically reviewed the manuscript for important intellectual content.

Dr Shabarek and Dr. Amin substantially contributed to the initial acquisition of data, drafted the initial manuscript, and reviewed, revised and prepared the manuscript for submission.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

***Cite this article:*** Genetic Heterogeneity in a Multigenerational West Virginia Family for Periodic Fever Syndrome; Am J of Nep and Ther. 2021; 4(1): 01-09.

## References


1. Sarkisian T, Ajrapetian H, Beglarian A, et al. Familial Mediterranean fever in Armenian population. Georgian Med News. 2008:105
2. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med. 1967;43:227
3. Mache C, Goriup U, Fischel-Ghodsian N, Chen X, Schwingshandl J. Autosomal dominant familial Mediterranean fever-like syndrome. Eur J Pediatr.1996;787-790
4. Karenko L, Pettersson T, Roberts P. Case report: autosomal dominant Mediterranean fever in a Finnish family. J Intern Med.1992;232:365-369
5. Getz M, Pettit R, Perrault J, Kyle R. Autosomal dominant familial Mediterranean fever-like syndrome with amyloidosis. Mayo Clin Proc.1987;62:1095-1100
6. McDermott MF, Aksentijevich I, Galon J, et al. Germline mutation in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes.Cell.1999;97:133-144
7. Lachmann HJ, Papa R, Gerhold K, et al. The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EUROTRAPS international registry. Ann Rheum Dis.2014;63:2160
8. Tumor necrosis factor receptor-associated periodic syndrome. Genetics Home Reference.2011



***Cite this article:*** Genetic Heterogeneity in a Multigenerational West Virginia Family for Periodic Fever Syndrome; Am J of Nep and Ther. 2021; 4(1): 01-09.