Plant Archives Vol. 20, Supplement 2, 2020 pp. 2905-2910 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

DETERMINATION OF GENETIC MUTATIONS THAT EFFECT UMOD GENE IN CHRONIC RENAL FAILURE AT NINEVEH CITY, IRAQ

Eyman T. Al-Ali and Muna H. Jankeer
Biology Department, Science College, Mosul University, Iraq

Abstract

The current study was conducted at Al-Salam Teaching Hospital in Nineveh City for the period between 1/2/2018 and 1/5/2018. It aimed at identifying the mutations that cause chronic kidney failure in the UMOD gene in patients. This study included Follow-up of 95 patients according to a questionnaire containing the information for each patient, after which the DNA was extracted from the blood samples of patients with chronic renal failure and by using the technique of heterogeneity restriction for polymerase Chain Reaction Restriction Fragment Length Polymerase (RFLP-PCR), genetic polymorphism was determined. For the UMOD gene, a Nucleotides sequence determination technique was used of the enlarged segment using the Sequencing nucleotide reader device. The results showed that no interruption by means of categorical enzyme (THIII) occurred. As for the results of sequencing, a number of genetic variations of the enlarged segments were determined by polymerase chain reaction

Keywords: Chronic Kidney Failure, UMOD Gene, Uromodulin, PCR, Sequence Determination.

Introduction

Kidney diseases are among the most common causes leading to death in many countries around the world. Kidney diseases can be divided into two types: Acute Renal Failure (AFR) and Chronic Renal Failure (CRF) (Al Hilali, 2018). Chronic kidney failure leads to a gradual loss of kidney function over a long period of time that may be a month or years. CRF is also known as the continuous destruction of renal functional units (Nephrons), coinciding with the symptoms of unspecified kidney degradation until advanced stages are reached up to the fifth stage which is known as the End Stage of Kidney Disease (ESKD). It is largely synonymous with the term chronic kidney failure (KDiGo 2009; 2013; National kind. 2002; Henry, 2001). The prevalence of this disease is increasing in the world and this increase exceeds those reported by various countries, where huge and rapid changes in lifestyle, massive population growth, rapid rise in life expectancy and the great urbanization occurred in recent years have made various cases of chronic kidney disease. It is expected that this disease will be associated with the spread of several diseases that have an effect such as a risk factor such as diabetes, hypertension and obesity (Ahmed *et al.,* 2014a; 2014b; Al - Sayyari & Shaheen 2011).

Genetic analysis demonstrated that a mutation in the UMOD gene caused a prevalent physical disease condition diagnosed by finding cysts in the region of the kidney core, inflammation of the inner tubules, high level of uric acid and it was accompanied by gout. The disease progresses to the last stage of chronic kidney disease, which is kidney failure (Sian *et al.,* 2009; Lens *et al.,* 2005; Ramopoldi *et al.,* 2003). This gene is known by other names: ADMCKD2, FJH, HNFJ, HNFJ1, MCKD2, THGP, THP (Ramopoldi *et al.,* 2003).

The UMOD gene is made up of 11 Axon encoded pieces. Exons are (2-11) encoded (Pennica *et al.,* 1987) to produce Uromodulin (UMOD). Euromodulin, also called Tamm Horsfall, is the most abundant protein in the urine. Under natural conditions, this protein was first purified in the 1950's, and since then it has been highlighted, but only slightly, on the importance of this protein. However, so far, the remainder of the physiological functions of this protein has not been identified. This protein consists of 640 amino acids, including 24 amino acids containing peptide at the nitrogenous end, 48 cysteine and 8 amino ends for association with glycated groups (Pennica *et al.,* 1987; Tamm-Horsfall, 1952) seven of which are related (Sian *et al.,* 2009; Kummar, 1990). The amino acid sequence indicates the possibility that uromodulin may contain growth factors in the form of specific clusters, of which the second and third contain calcium binding factors. The region of the second cysteic acid (D8C) is within the zinc rich region and the Zona Pellucida (ZP) region which is responsible for the polymerization of extracellular proteins into helical strands (Yong *et al.,* 2009; Serafin *et al.,* 2003).

Materials and Methods

During this study, (95) blood samples were collected from males with chronic kidney failure whose ages ranged between (15-70) years and who were subjected to hemodialysis weekly. They also proved their pathological condition through conducting functional tests for the kidney and periodically reviewing the department of kidney failure at Al-Salam Teaching hospital in the province of Nineveh. As 1.5 ml of blood was taken, and it was placed in container tubes on an anticoagulant (EDTA), and then the DNA was extracted. The DNA was isolated from the blood for all the samples included in the study, which are 95 samples depending on the method modified by (Iranpur and Esmailizadeh, 2010).

DNA extraction

DNA was extracted from the blood of all the samples included in the study using the method modified by (Iranpur & Esmailizadeh, 2010).

The solutions used in the extraction were:

1. Ethylene Diamine Tetracetic Acid EDTA solution with a concentration of 0.5M and of 8.0.Weighing 186.1 g of EDTA powder and dissolved in 800 ml of distilled water. The acid function was set at pH 8, completed the volume to 1 liter of distilled water and sterilized the

solution in a sterile or autoclave at 141 ° C and under pressure 1 for 15 minutes.

1. 2.Toris-HCl gear solution with a concentration of 1 molar and a 7.6 acidic switch , dissolved 121.1 g of Tris-HCL in 800 ml of distilled water and set the acidic function at 7.6 pH and completed the volume to 1 liter of distilled water. Then the solution was sterilized in the sterile or autoclave at a temperature of 121 ° C and under 1 atmosphere for 15 minutes.
2. Red Blood Cell Lysis Buffer regulating solution consisting of Tris-HCL solution with a concentration of 0.01M, sucrose at a concentration of 320M, magnesium chloride 2 MgCl at a concentration of 25M and Triton - 100X at a concentration of 1%. This solution was prepared by adding 10 mL of the buffer solution at a concentration of 0.01 M and adding 109.54 g of sucrose, 1.01 g of magnesium chloride and (10) mL of Triton-x 100 to 800 mL of distilled water. The acidic function was set at pH 8.0, and then completed the volume to 1 liter of distilled water, sterilized the solution using the reagent at 121 ° C and press 1 atmosphere for 10 minutes.
3. Nucleic Lysis Buffer buffer solution. This solution consists of Tris-HCL solution with a concentration of 0.01M and sodium citrate at a concentration of 11.4M and EDTA at a concentration of 1M and Sodium Dodecyl Sulphate (SDS) at a concentration of 1%. This solution was prepared by adding 10 ml of Tris-HCl at a concentration of 0.01M, 3.75g of EDTA and 10g From SDS and 2.94 g of sodium citrate to 800 ml of distilled water. The acid function is set at pH 8.0 and volume is supplemented to liters with distilled water, sterilized the solution in the conduct or at 121 ° C and compressed for 15 minutes.
4. TE Buffer solution: this solution was prepared by withdrawing 5 ml of 1 Tris – HCl pH 7.6 and 2 ml of EDTA solution with a concentration of 0.5 and an acidic switch 8 and complete the volume to a liter of distilled water. The acid function was set at 8.0 and the sterility of the solution was kept at a temperature of 121 ° C for a period of 15 minutes.
5. Chloroform
6. Ethanol (100%), -20

DNA extraction method

1. 500 µl of blood was placed in a 1.5 ml tube, and an additional 1 ml of regulating solution for the red blood cells analysis was added to it, and mixed quietly with the Vortex apparatus.
2. Centrifugation of the tube in the microfuge was performed at a speed of 7000 rpm for two minutes, the filtrate was eliminated, and the previous plan was repeated 1-3 times for eliminating hemoglobin and the tube was placed on the filter paper upside down for several seconds.
3. 400 µl of buffer solution for nucleic lysis was added to the tube and mixed quietly.
4. Added 100 µl of NaCl at a concentration of 5M saturated, add 600µ l of chloroform to that tube and mix quietly, then centrifuge that tube in the Microfuge at 7000 rpm for two minutes.
5. Withdrew 400 µl of the filtrate, place in a clean and dry tube, add 800 µl of cold ethanol, and mix the contents quietly. In this stage, DNA bundles are obtained as white strands.
6. Centrifuge the tube in the Microfuge at a speed of 12000 rpm for one minute, then the leachate is removed and the tube was allowed to dry at room temperature.
7. 50 µl of the TE solution was added to the extracted DNA and mixed quietly and the sample was preserved at -20 ° C until use.

Determination of extracted DNA purity and concentration

The purity and concentration of DNA extracted from blood samples was estimated in this study using Nano drop device.

Electrical migration

Solutions used in the electric relay process

1. TBE 10 solution with a power of X10: A TBE solution prepared from the English company Lonza consisting of one liter of X10 was used, using Tris-Base at a concentration of 0.89 molar, Boric acid at a concentration of 0.89 molar and Na2EDTA at a concentration of 0.02 molar. The acidic function of the solution was set at 8.3.
2. Loading Buffer with a concentration of X10, prepare by dissolving 0.25 g of bromophenol blue in the glycerol at a concentration of 50%, add EDTA at a concentration of 60 mmol and an acid exchange of 8.0 and completed the volume to 100 ml of distilled water.
3. Ethedium bromide dye was prepared by dissolving 100 mg of dye powder in 10 ml of distilled water and kept in a sterile vial at 4 ° C until use.

Preparation of the agarose gel and the electrophoresis process of DNA

To move and detect genomic DNA, the agarose gel is prepared with a concentration of 1%. To obtain this concentration, 0.5 g of agarose powder was dissolved in 50 ml of X10 TBE using a heat source with constant stirring until boiling and then left for cooling to a temperature of (60-50) C°. The agarose gel solution was poured into the tray sink of the electrostatic relay device after the wells comb was installed at the edges of the gel and the casting was quietly to avoid bubbles formation, and that they should be removed using the pipette, then the gel was left for the purpose of hardening. The tray was placed in an electrostatic relay containing X10 TBE solution and then quietly raised the comb. Relay samples were prepared by mixing 5 µl of the DNA sample with 3 µl of loading solution. The relay is switched on by operating a voltage of 5 V \ Cm and the process takes (2-1.5) hours. After completing the deportation process, the gel was transferred to a basin containing the dye of ethidium and left for 45 minutes with continuous stirring. Then the gel was imaged under ultraviolet radiation using a gel documentation device to be able to see the DNA bundles and the output of the PCR reaction.

PCR - REFLP interactions

The DNA concentration was adjusted in all samples studied by dilution by TE to obtain the required

concentration for conducting PCR reactions and was 25 ng\µl for each sample.

The Master Reaction main reaction mixture for each PCR reaction was prepared by mixing the DNA sample and the initiator of the UMOD Renal Failure gene with the Pri Mix components inside the 0.2 ml tube that is equipped by Promega USA. The reaction volume was then set to 20 µl with distilled water, and the mixture is put in a device Microfuge for a period of (3-5) seconds to complete the mixing of the reaction components. The tubes must be placed inside the ice during work, after which the reaction tubes were inserted into the Thermocycler to conduct the reaction using the special program for each reaction. The PCR reaction was incubated with the enzyme that breaks the mutation UMOD gene for half an hour at a temperature of 65 °C. Then the sample was loaded into the pre-prepared agarose gel at a concentration of 2% with the volumetric guide ladder DNA prepared from Biolaps. Then the samples were carried over by operating the electrophoresis device for a period of (75-90) minutes and then the gel was stained and immersed with the dye of ethidium bromide for a period of (30-45) minutes with stirring, and finally the gel was imaged using the Gel documentation device.

Detection of a mutation in the UMOD gene

The presence of the mutation was detected in 95 samples, as 100 ng of molded DNA and 10 micromoles of the initiator of the mutation supplied by Alpha were added to the Pri Mix contents.

Forward	5" – GTG TTG TCA TCT CCT CAG GAT TA – 3"
Reverse	5"- CTG TTT GGG AAG AGG AGT CGA TA- 3"

The reaction tubes were inserted into the Thermocycler to conduct the reactive reaction using the special program of the reaction as shown in the following table:

No.	Stage	Temperature	time	Cycle number
1.	Initial denaturation	95	5 min.	1
2.	Denaturation	95	1 min.	35
3.	Annealing	63	1.5 min.	
4.	Extension	72	1.5 min.	
5.	Final extension	72	7min.	1
6.	Stop reaction	4	5 min.	1

After the reaction was completed, the tubes were removed from the polymerization apparatus with the output of pb949, and 5 µl was withdrawn and incubated with the categorical enzyme (THIII) at a concentration of 5 units prepared by Biolaps for a period of 30 minutes at a temperature of 65 ° C (Alhassani, 2013).

Results and Discussion

The results showed that the categorical enzyme (THIII) did not recognize the location of the mutation in the amplified segment, as the reaction result of 110BP before digestion and after digestion with the categorical enzyme was similar, as shown in Figure 1.

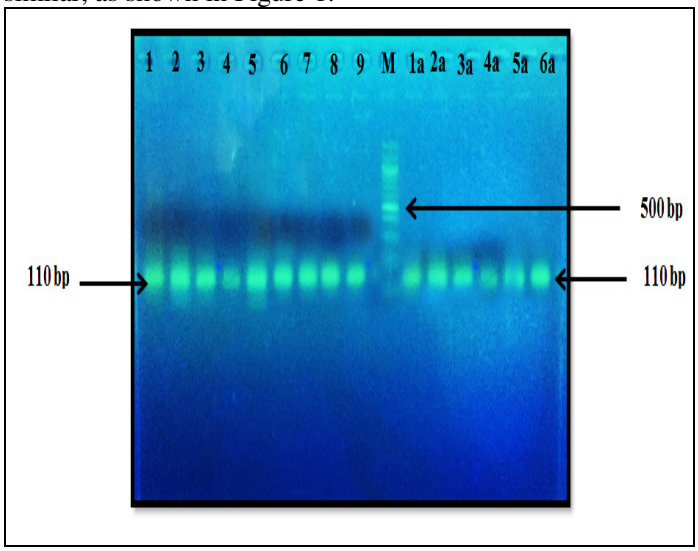

Figure 1 shows the output of the PCR of the UMOD gene, since M represents the volumetric evidence and the samples (1,2,3,4,5,6,7,8,9) represent the reaction result in a size of 110 bp while the samples (1a , 2a, 3a, 4a, 5a, 6a) they represent the reaction product after being treated with the THIII categorical enzyme, as no cut of the amplification product of 110 bp has occurred. Which was carried over in the agarose gel at a concentration of 2%.

Therefore, a test was conducted for the sequence of nitrogenous bases of the amplified beam resulting from the PCR interaction. The results in Figure (2) show the presence of three locations for changes in the sequence of nucleotides in the amplified segment compared with the original gene sequence in the NCBI site. It also show the frequency of change in the sequence of 3462 in two From the samples where the nitrogen base was replaced by cytosine C to thymine T.

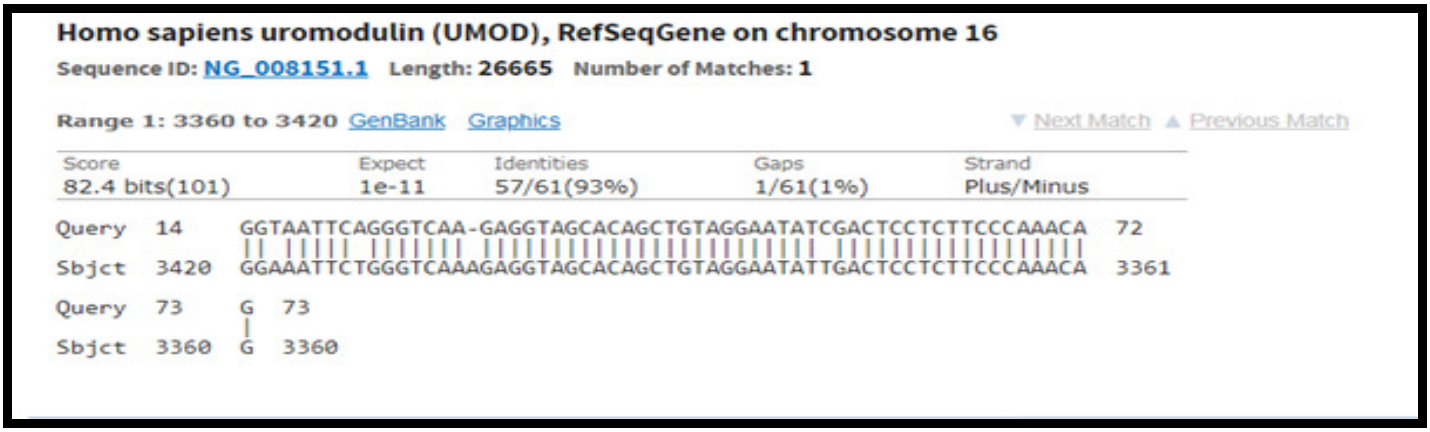

Fig. 2 : Shows the percentage of match between the samples on which the nucleotide sequence test was performed compared to the UMOD gene sequences in the NCBI.

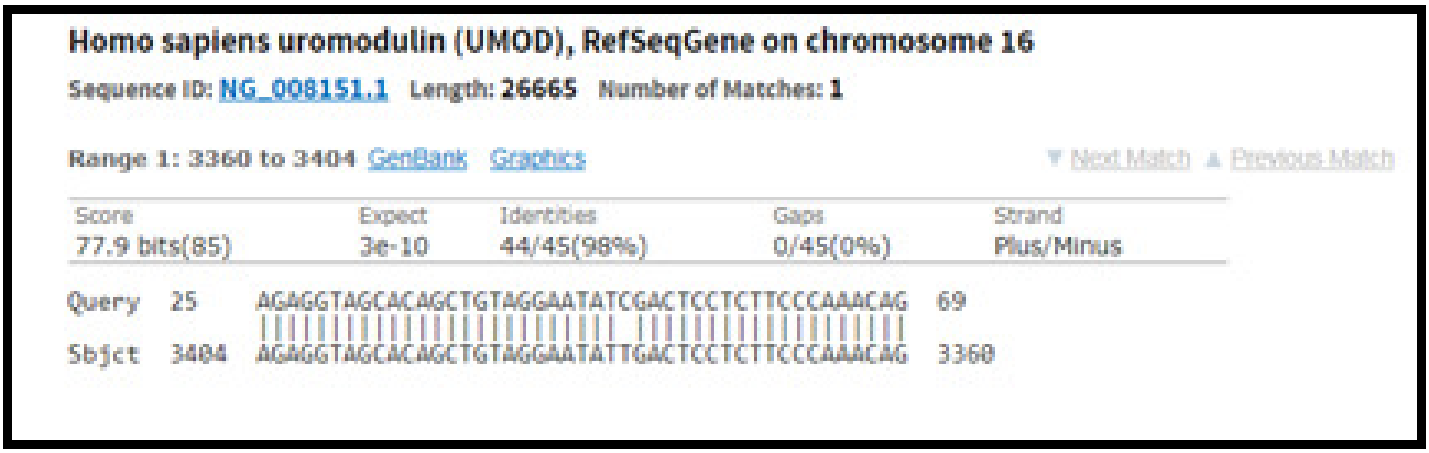

Fig. 3 : shows the frequency of the variation in the sequence 3262 from the nitrogenous base cytosine C to thymine T.

From the above figures we have several differences, as shown in the table below:

Sample	Nucleotide	Location	Sequence ID	Gaps	Expect	Identity
1	T → A	3423	NG-008151.1	1\61	3e-10	93%
2	A → T	3429	NG-008151.1	1\61	1e-10	95%
3	C → T	3462	NG-008151.1	0\45	1e-11	98 %

In the current study, when comparing the sequence of the nitrogenous bases of the amplified segment and the sequences of the original gene, it was observed that these variations occurred in the sequence of the second intron site of the gene within the sequence (3420 >> 3360). The second intron sequences start in the gene from 2230 and end in 3666 sequence. Samples were taken for two patients who suffer from chronic kidney failure disease associated with kidney stones and high blood pressure. One of them has diabetes. Due to the lack of studies that link chronic kidney disease to the genetic factor and determine the mutations in the UMOD gene that cause UMOD-related kidney disease, it was not automatically agreed that any of the variants has any effect on the gene completely. Since the variance diagnosed in this study is of a single nucleotide polymorphism (SNP) type. However, variations in the process of cloning into an RNA from the intron include formations or formulas. There are many ways to organize genes. The variations that occur in the sequence of the intron rules may affect the successive binding of the mRNA pieces (such as linking of receiving or donor sites, secondary structure, etc.). Variations in the sequence of intron bases can also act as enhancers, which can act on the gene in which they are present, or can enhance the expression of many genes. Therefore, you can look at the expected protein binding sites and see if there is any differential binding to a specific protein. But if there is no evidence to believe this intron has a regulatory effect, it is important not to assume that the SNP is effective. Remember that SNP can bind to some groups because it is bound to another SNP that has a physical effect on gene regulation. We can say that the occurrence of this heterogeneity in the intron region and its repetition has been attributed to the fact that this intron has a regulatory effect on the formation of the uromodulin protein, which causes the emergence of a condition of kidney disease that develops from hyperuricemia, kidney stones, high blood pressure and up to the last stage of this state, which is chronic kidney failure.

The genetic study relied on the UMOD gene sequence and mutation detection, with about 60 mutations described so far (Rampoldi *et al.,* 2011; Bollee *et al.,* 2001; Wolf *et al.,* 2006; Lens *et al.,* 2005). Since the majority of mutations are on the exons 3 and 4 of the gene, it is usually studied in most research, although mutations have also been described in other Exons, such as Exon 7. 19 No clear association has been found between phenotype and genotype. (Scolari *et al.,* 2004; Lhotta *et al.,* 2012; Bollee *et al.,* 2011;). Williams *et al.,* 2009 indicated that 90% of mutations are in amino acid substitution and 62% of them alter cysteine sites, which leads to changes in the protein folding process. The UMOD gene is regulated by many transcription factors, including HNF1b, whose mutation is responsible for another disease of hyperuricemia that should be suspected in cases with clinical presentation consistent with chronic kidney failure (Faguer *et al.,* 2011; Zaucke *et al.,* 2010; Wolf *et al.,* 2009). It causes mutations in the UMOD gene (chromosome region 16) two types of disorders are tubular nephropathy with a predominant autosomal genotype and type two cystic-mediated cystic kidney disease. With hereditary hyperuricemia, these disorders are currently included under the term "kidney disease caused by the UMOD gene mutation" (Ahmed *et al.,* 2014; Ayasreh-Fierro *et al.,* 2013; Bleyer *et al.,* 2011;) Kidney disease caused by a mutation in the UMOD gene has a very low prevalence rate, less than 1% of end-stage kidney disease (ESKD) in adults and this proportion corresponds to a lack of diagnosis of this relationship (Coto García, 2011). Ayasreh-Fierro *et al.,* 2013 indicated that the proportion of people with a mutation in the UMOD gene in their study sample of patients with uric acidosis was 12.5% of cases. Uromodulin deficiency causes tubular re-absorption deficiency causing increased urea and hyperuricemia (Moro *et al.,* 1991), in kidney disease associated with UMOD gene mutations Kidney failure develops slowly, generally reaching the final stage between the fourth and sixth decades of life (Bollee *et al.,* 2001; Scolari *et al.,* 2004;) Inherited cases of MCKD1-associated kidney failure usually have a higher level of hyperuricemia and increased early and recurrent gout attacks, and ultimately lead to end-stage renal failure. Early in life, although there are various causes of chronic kidney disease and failure for chronic renal hereditary factors are often excluded as chronic kidney disease is a lifelong disorder that is associated with the disease. And the death of large numbers of people around the world is due to the complications of gradual loss of

kidney function and eventual kidney failure. Early diagnosis and detection of the causative factors are important to improve the health outcomes of patients with chronic kidney disease, mutations in the gene that encodes uromodulin protein lead to prevalent and rare physical diseases, collectively referred to as kidney disease related to uromodulin. They are characterized by gradual tubular damage, impaired kidney ability to increase urine concentration, hyperuricemia, renal cysts, and progressive kidney failure. Recent studies indicate that the accumulation of mutant uromodulin within the cells of the living body is a major cause of chronic kidney failure. Recently, genomic correlation studies have identified Uromodulin as a risk factor for chronic kidney disease (CKD) and hypertension (Fugiel *et al.,* 2013). Several studies were conducted around the world about the extent of this gene's association with chronic kidney disease syndrome, and among these studies was a study by Ahmed and others 2017 on 103 Saudi kidney failure patients who reached an important conclusion, which is that the rate of mutation recurrence in the UMOD gene in patients with kidney failure was 9.7 % of these patients.

Conclusions

Mutations in the UMOD gene cause a disease characterized by excess uric acid, gout, and kidney disorders. The proportion of cases where mutations were detected was 2% of the total in the second intron, which could be considered a regulatory intron for the gene to function.

References

Ackerman, E. and Brill, A. (1974). Xanthine oxidase activity in methods of enzymatic analysis, Ed. Bergmeyer. H.V. and Ed. Academic press. Inc. USA., 3(6): 277-280.

Ahmed, H.G.; Ginawi, I.A. and Al–Hazimi A.M. (2014) Prevalence estimates of Chronic Kidney Disease in Hail Region, KSA: in a comprehensive Survey. International Journal of Science and Research. 3(7): 252–256.

Ahmed, H.G.; Ginawi, I.A. and Al-Hazimi, A.M. (2014). Prevalence of Hypertension in Hail Region, KSA: in a Comprehensive Survey. International Journal of Sciences: Basic and Applied Research 17(2): (B).

Alaygut, D.; Torun-Bayram, M.; Soylu, A.; Kasap, B.; Türkmen, M. and Kavukçu, S. (2013). Chronic kidney disease in an adolescent with hyperuricemia familial juvenile hyperuricemic nephropathy. Turk J Pediatr.; 55: 637–640.

Alhassani, O.M. (2013). Biochemical and Genetic Study For Newborn With Galactosemia that caused by GALT Gene MAutation in Nineveh Province. A Ph. D. Thesis . University of Mosul, College Biology.

Alhelali, L. (2018). Oxidative Stress in Health and Disease .Yazori Puplisher, 1est paint. Amman, Jordan.

Al-Sayyari, A.A. and Shaheen, F.A. (2011). End stage chronic kidney disease in Saudi Arabia. A rapidly changing scene. Saudi Med J., 32(4): 339- 346.

Anthony, M.; Esparaz, M.D.; Jeffrey, A.; Pearl, M.D.; Brian, R.; Herts, M.D.; Justin LeBlanc, M.D. and Baljendra Kapoor, M.D. (2015). FSIR Iatrogenic Urinary Tract Injuries: Etiology, Diagnosis, and Management, Semin Intervent Radiol.; 32(2): 195–208.

Arkill, K.P.; Qvortrup, K.; Starborg, T.; Mantell, J.M.; Knupp, C.; Michel, C.C.S.; Harper, S.J.; Salmon, A.H.J.; Squire, J.M.; Bates, D.O. and Neal, C.R. (2014). Resolution of the three dimensional structure of components of the glomerular filtration barrier. BMC Nephrology 15: 24.

Bleyer, A.J. (2009). Improving the recognition of hereditary interstitial kidney disease. J Am Soc Nephrol; 20(1):11-3.

Bollee, G.; Dahan, K.; Flamant, M. and Moriniere, V. (2011). Phenotype and outcome in hereditary tubulointerstitial nephritis secondary to UMOD mutations. Clin J Am Soc Nephron; 6: 2429–2438.

Bollee, G.; Dahan, K.; Flamant, M.; Moriniere, V.; Pawtowski, A. and Heidet, L. (2011). Phenotype and outcome in hereditary tubulointerstitial nephritis secondary to UMOD mutations. Clin J Am Soc Nephrol; 6(10): 2429-38.

Coto García E. (2011). Enfermedad renal quística medulary nefronoptisis. Nefrologia; 2(1):74-9.

Faller, A.; Scheunke, M. and Scheunke, G. (2014). The Human Body : An Introduction to Structure and Function. Printed in Germany by Grammlich, Pliezhausen.

Fugiel, A.; Kuzniewski, M. and Fedak, D. (2013). Uromodulin can it be a new marker of kidney damage?. PrzeglLek 70(11): 976-982.

Graaff, Van De (2002). "Human Anatomy, Sixth Edition". New York: McGraw-Hill.Smith, Peter (1998). Internet reference, Role of the Kidney [2]. Department of Clinical Dental Sciences, University of Liverpool.

Hart, T.C.; Gorry, M.C. and Hart, P.S. (2002). Mutations of the UMOD gene are responsible for medullary cystic kidney disease 2 and familial juvenile hyperuricemic nephropathy. J Med Genet 39: 882-892.

Hart, T.C.; Gorry, M.C. and Hart, P.S. (2002). Mutations of the UMOD gene are responsible for medullary cystic kidney disease 2 and familial juvenile hyperuricaemic nephropathy. J Med Genet. 39(12): 882–892.

Hart, T.C.; Gorry, M.C.; Hart, P.S.; Woodard, A.S.; Shihabi, Z.; Sandhu, J.; Shirts, B.; Xu, L.; Zhu, H.; Barmada, M.B. (2002). Mutations of the UMOD gene are responsible for medullary cystic kidney disease 2 and familial juvenile hyperuricemic nephropathy. J Med Genet 39: 882-889.

Henry, J.B. (2001). Clinical diagnosis and management by laboratory methods, 20th Ed., w.b. saunders company, a harcourt health sciences company, philadelphia. 159-177.

Iranpur, V. and Esmailizadeh, A. (2010). Rapid Extraction of high Quality DNA from whole blood Stored at 4°C for Long Period. Department of animal Science, Faculty of Agriculture, Shahrekord University, Shahrekord, Iran. www.protocol-online.org.

Jeanpierre, C.; Whitmore, S.A. and Austruy, E. (1993). Chromosomal assignment of the uromodulin gene (UMOD) to 16p13.11. Cytogenet Cell Genet., 62(4):185–1.

KDIGO: Kidney Disease Improving Global Outcomes (2009) KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int 76 (Suppl 113.).

KDIGO: Kidney Disease Improving Global Outcomes (2009). KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int 76 (Suppl 113).

Lens, X.M.; Banet, J.F.; Outeda, P. and Barrio-Lucia, V. (2005). A novel pattern of mutation in uromodulin disorders: autosomal dominant medullary cystic kidney disease type 2, familial juvenile hyperuricemic nephropathy, and autosomal dominant glomerulocystic kidney disease. Am J Kidney Dis., 46: 52–57.

Lens, X.M.; Banet, J.F.; Outeda, P.; Barrio-Lucia, V. (2005). A novel pattern of mutation in uromodulin disorders: autosomal dominant medullary cystic kidney disease type 2, familial juvenile hyperuricemic nephropathy, and autosomal dominant glomerulocystic kidney disease. Am J Kidney Dis; 46(1): 52-57.

Liu, M.; Chen, Y.; Liang, Y.; Liu, Y.; Wang, S.; Hou, P.; Zhang, H. and Zhao, M. (2013). Novel UMOD mutations in familial juvenile hyperuricemic nephropathy lead to abnormal uromodulin intracellular trafficking. Gene; 531: 363–369.

Malakoutian, T.; Amouzegar, A.; Vali, F.; Asgari, M. and Behnam, B. (2016). First report of familial juvenile hyperuricemic nephropathy (FJHN) in Iran caused by a novel de novo mutation (E197X) in UMOD. J Mol Genet Med.; 10(2): 218.

Moro, F.; Ogg, C.S.; Simmonds, H.A.; Cameron, J.S.; Chantler, C.; McBride, M.B.; Duley, J.; Davies, P. (1991). Familial juvenile gouty nephropathy with renal urate hypoexcretion preceding renal disease. Clin Nephrol 1991; 35(6):263-9.

National Kidney Foundation (2002). K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 39(2 Suppl 1): S1-266.

Pennica, D.; Kohr, W.J. and Kuang, W.-J. (1987). Identification of human uromodulin as the tamm-horsfall urinary glycoprotein, Science, 236(4797): 83–88.

Rampoldi, L.; Scolari, F.; Amoroso, A.; Ghiggeri, G. and Devuyst, O. (2011). The rediscovery of uromodulin (Tamm-Horsfall protein): from tubulointerstitial nephropathy to chronic kidney disease. Kidney Int. : 80(4):338-47.

Rampoldi, L.; Scolari, F.; Amoroso, A.; Ghiggeri, G. and Devuyst, O. (2011). The rediscovery of uromodulin (Tamm-Horsfall protein): from tubulointerstitial nephropathy to chronic kidney disease Kidney Int.; 80: 338–347.

Scolari, F.; Caridi, G.; Rampoldi, L.; Tardanico, R.; Izzi, C.; Pirulli, D.; Amoroso, A.; Casari, G. and Ghiggeri, G. (2004). Uromodulin storage diseases: clinical aspects and mechanisms. Am J Kidney Dis.; 44(6): 987-99.

Serafini-Cessi, N.; Malagolini and Cavallone, D. (2003). Tamm-Horsfall glycoprotein: Biology and clinical relevance, American Journal of Kidney Diseases, 42(4): 658–676.

Sian, E.P.; Anita, A.C.; Reed, J.G. and Rajesh, V.Th. (2009). Uromodulin mutations causing Familial Juvenile Hyperuricaemic Nephropathy lead to protein maturation defects and retention in the endoplasmic reticulum. Human Molecular Genetics 18(16): 2963-74.

Tamm and Horsfall Jr., F.L. (1952). A mucoprotein derived from human urine which reacts with influenza, mumps, and Newcastle disease viruses, The Journal of Experimental Medicine, 95(1): 71–97.

Wei, X.; Xu, R.; Yang, Z.; Li, Z.; Liao, Y.; Johnson, R.; Yu, X.; Chen, W. (2012). Novel uromodulin mutation in familial juvenile hyperuricemic nephropathy. Am J Nephrol. 36: 114–120.

Wolf, M.T.; Mucha, B.E.; Hennies, H.C.; Attanasio, M.; Panther, F.; Zalewski, I.; Karle, S.; Otto, E.; Deltas, C.; Fuchshuber, A. and Hildebrandt, F. (2006). Medullary cystic kidney disease type 1: mutational analysis in 37 genes based on haplotype sharing. Hum Genet; 119(6): 649-58.

Yang, H.; Wu, C.; Zhao, S. and Guo, J. (2004). Identification and characterization of D8C, a novel domain present in liver-specific LZP, uromodulin and glycoprotein 2, mutated in familial juvenile hyperuricaemic nephropathy. FEBS Lett., 578: 236–238.

Zaucke, F.; Boehnlein, J.M.; Steffens, S.; Polishchuk, R.S.; Rampoldi, L.; Fischer, A. (2010). Uromodulin is expressed in renal primary cilia and UMOD mutations result in decreased ciliary uromodulin expression. Hum Mol Genet;19(10):1985-97.