Role of ATP Binding Cassette Subfamily G Member 2 (ABCG2) Gene Mutation (rs2231142) in Hyperuricemia and Gout in Egyptian Population

Original Article

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ABSTRACT

Background: Hyperuricemia means increased serum uric acid levels in the blood. Meanwhile, the immune system responds to monosodium urate crystals that precipitate in synovial fluid, resulting in gout, an inflammatory arthritis. ATP Binding Cassette Subfamily G Member 2 (ABCG2) protein is a uric acid transporter responsible for excretion of uric acid through intestine and kidneys. A common polymorphism (rs2231142) in the (ABCG2) gene is correlated with elevated serum uric acid concentration causing hyperuricemia and gout.

Objective: To assess the role of ABCG2 gene single nucleotide polymorphism in hyperuricemia and gout in Egyptian population.

Patients and Methods: This research has been performed on eighty subjects engaged from Ain Shams University Hospitals, Internal medicine department, outpatient clinics. Subjects of the research have been subdivided into 2 groups: Group I, involved sixty (60) cases which is further subdivided into 2 subgroups. Group (Ia) which includes thirty (30) cases with gout, group (Ib) which includes thirty (30) patients with hyperuricemia and a sex and age matched group Π which includes twenty (20) healthy individuals. An informed verbal consent has been attained from all recruited subjects and under the approval of the Research Ethics Committee of Ain Shams University.

Results: The current investigation demonstrated that the (GG) genotype and the (G) allele frequencies were more prevalent in healthy controls than in cases. In contrast to healthy controls, cases showed a greater incidence of the (TT) and (GT) genotypes, in addition to the (T) allele.

Conclusion: The current investigation showed the presence of a significant correlation among the ABCG2 (rs2231142) 421 G/T polymorphism and development of gout with GT genotype. Though, it pointed to the probability of presence of elevated probability of progress of gout and hyperuricemia with T allele. Additional investigations with greater sample size are required to explain the correlation.

Key Words: ABCG2, hyperuricemia, mutations, (rs2231142), real time PCR.

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INTRODUCTION

Hyperuricemia means elevated serum uric acid levels more than 7.0 milligram per deciliters (416 µmol/L) in males and postmenopausal females, and 5.7 milligram per deciliters (339 µmol/L) in premenopausal women[1]. Gout is a systemic disease and is the most frequent form of inflammatory arthritis results from the deposition of needle like structures called monosodium urate crystals (MSU) in joint synovial fluid[2].

Hyperuricemia and gout are increasing particularly in developed nations with a western lifestyle. There are an assessed forty-one million individuals global with gout[3]. A cross-sectional research was conducted in Egypt to evaluate the occurrence of hyperuricemia in 200 elderly cases who were hospitalized and to determine its correlation with the metabolic disorder. The results showed that hyperuricemia prevalence was 21.0% in elderly males and 15.1% in elderly females[4]. Gout prevalence in Egypt in 2019 was 1–4% and incidence rate 0.1–0.3% of the general population[5].

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There are many risk factors of hyperuricemia and gout as dietary factors, medications and genetics. Factors like diet have been showed to be ≤0.3% of the difference within serum uric acid concentrations however genetics represented 23.9% of the difference which means that diet has fewer impact on hyperuricemia probability compared to genetics[6].

Uric acid transport variation has a major part in the pathogenesis of gout and hyperuricemia. There are many genetic loci of uric acid transporters which are responsible for difference within serum uric acid concentrations and development of gout. These transporter genes are (ABCG2) gene encoding ABCG2 protein transporter, Solute Carrier Family 2 Member 9 gene (SLC2A9) encoding GLUT9, (SLC17A1) gene encoding NPT1 and (SLC22A12) gene encoding URAT1[7].

The ABCG2 transporter has been found in many organs as in the small intestine, kidneys, blood-placenta barrier and liver cells. The transporter is recognized to control the exit of different compounds across the cell membrane as uric acid. A common mutation in ABCG2 gene (rs2231142) is correlated with increased serum uric acid concentration and decreased renal excretion of uric acid[8].

PATIENTS AND METHODS

Study participants

This observational case control research has been performed on sixty patients. They were recruited from the out-patient clinic of department of Rheumatology and Rehabilitation at Ain Shams University Hospitals. They were diagnosed in accordance with the criteria of the American College of Rheumatology (ACR)[9]. 20 age- and gender- corresponding healthy participates were classified as healthy control group. All laboratory work has been conducted in the Clinical Pathology Department, Ain Shams University Hospitals.

Group I: (Patient`s Group): This group is further subdivided into

Group Ia (Gout patients): This subgroup consists of thirty (30) patients, they were classified into twenty-five (25) males and five (5) females ranging in age between 24 and 79 years diagnosed in agreement with the criteria of the American College of Rheumatology (ACR).

Group Ib (patients with hyperuricemia): This subgroup consists of thirty (30) patients, they were twelve (12) males and eighteen (18) females ranging in age between 26 and 79 years. They were identified by an abnormally increased blood uric acid level, which was typically greater than seven milligram per deciliter in males and six milligram per deciliter in females.

Group II (Control Group): Twenty (20) Age and sex corresponding healthy people, recruited randomly for yearly health check with no family history of gout.

ETHICAL APPROVAL

The Research Ethics Committee of Ain Shams University provided approval to the research with assurance NO, following the gathering of informed oral consent from each participant prior to their participation. (FMASU MS 280/2022).

Exclusion Criteria:

Female patients before menopause [Previous studies showed this mutation could be relatively less in people with elevated estrogen concentrations compared with those with low estrogen concentrations]

Patients with medical conditions that cause secondary hyperuricemia e.g

1. Myeloproliferative diseases or their treatment.
2. Therapeutic regimens that produce hyperuricemia.
3. Renal failure.
4. Renal tubular disorders.

Sampling:

Venipuncture was utilized to collect five milliliters of venous blood from each subject in a completely aseptic condition. Blood samples have been collected as follows:

1. A tripotassium ethylene diamine tetra acetate "k3 EDTA" vacutainer was used to place two milliliters of venous blood. The tube was inverted multiple times to ensure proper mixing and was inspected to rule out the presence of clots. All of the blood samples have been stored at minus twenty degrees Celsius until the time of analysis. The samples were not

frozen or thawed repeatedly till the deoxyribonucleic acid (DNA) extraction and identification of the ATP Binding Cassette Subfamily G Member 2 (rs 2231142) gene mutation by real-time polymerase chain reaction (RT-PCR).

2. To conduct an immediate chemistry analysis (including uric acid, triglycerides, total cholesterol, creatinine, blood urea nitrogen, and blood glucose) and CRP, three milliliters of venous blood have been collected on a plain tube containing gel for serum separation. The sample was centrifuged at 3000-4000 rpm for ten minutes to separate the serum, after allowing sample to clot at room temperature for fifteen to thirty minutes.

Genotyping

Genomic DNA has been extracted from EDTA anticoagulated peripheral blood using Thermo scientific DNA purification mini kit. Genotyping of ATP Binding Cassette Subfamily G Member 2 rs2231142 mutation was performed by TaqMan real time PCR. Amplification of the extracted gene was done utilizing DTlite real time PCR System utilizing readymade genotyping assay kit provided by ThermoFisher (Thermo scientific 168 Avenue Waltham, MA USA 02451.1) involving sequence specific forward primer, reverse primer and 2 fluorescents (VIC/FAM) labeled TaqMan probes with minor groove binder (MGB) for distinguishing between the two alleles of rs2231142 with sequence: 5'GCAAGCCGAAGAGCTGCTGAGAACT[G/T] TAAGTTTCTCTCACCGTCAGAGTG '3.Mutation: G/T, transversion substitution.

The allelic discrimination and the absence or presence of the mutation have been determined by the type of emitted fluorescence of either of the reporter dyes or the two simultaneously, as illustrated in (Table 1) and (Figure 1).

Table 1: Correlation between Fluorescence Sequences and Signals within Each Sample[10].

Fluorescence Increase	Indication
HEX dye fluorescence only (green)	Homozygosity for allele 1(Wild allele, G)
FAM dye fluorescence only (blue)	Homozygosity for allele 2(Mutant allele, T)
Fluorescence signals for both dyes	Heterozygosity for allele 1-allele 2

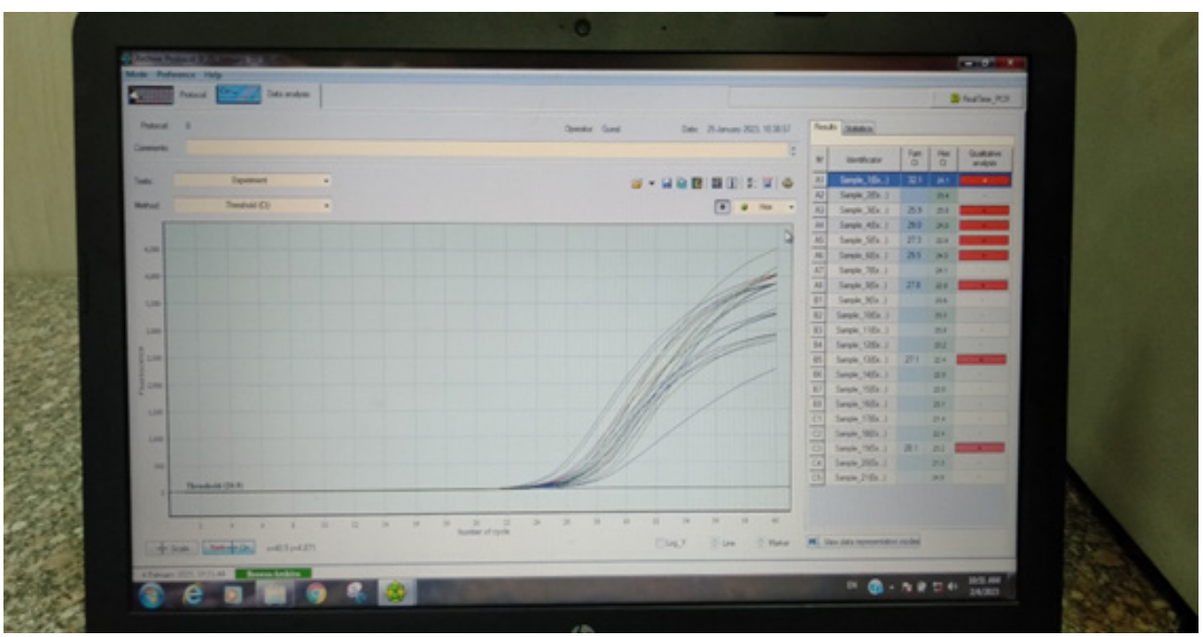

Fig. 1: Illustration of the principle of the real-time PCR allelic discrimination through different fluorescence emission.

Statistical data analysis

Data have been examined utilizing the Statistics Package for Social Sciences (SPSS) version 25. Data have been presented as Mean±Standard deviation (SD) for quantitative parametric measures, alongside median and percentiles for quantitative non-parametric measurements. The Kruskal-Wallis test was utilized to compare more than two cases groups for non-parametric data. The Chi-square test was utilized to compare two distinct sets concerning categorized data. The probability of 0.05 was defined significant, whereas 0.01 and 0.001 were regarded as highly significant.

RESULTS

This research has been performed on sixty subjects recruited from Ain Shams University Hospitals, Internal medicine department, outpatient clinics. Subjects of the research have been subdivided into 2 groups: Group I, included sixty cases which is further subdivided into 2 subgroups. Group (Ia) which involved thirty cases with gout, group (Ib) which includes thirty (30) patients with hyperuricemia and a sex and age matched group Π which includes twenty (20) healthy individuals. An informed verbal consent has been attained from all recruited subjects and under the approval of the Research Ethics Committee of Ain Shams University.

(Table 2) presents the descriptive and comparative statistics of the demographic and clinical data for groups in the research. where it shows that both group I and Π were age matched (H=5.07, p= 0.079). Highly statistically significant difference is discovered among examined groups according to gender (X^2 = 18.7, p-*value*< 0.001). Within group (Ia) there were 25 males (83%) and 5 females (17%). In group (Ib), there were 12 males (40%) and 18 females (60%). The male sex forming the majority of both patients and control groups. Statistically insignificant difference is discovered among examined groups according to age (p-*value* = 0.079). There is increased percentage of patients with hypertension (HTN) within group (Ia) and group (Ib) (n:15, 50%) (n:15, 50%) when compared with group Π (0 patient, 0%) (X^2 =16, p< 0.001). There is increased percentage of patients with positive family history in group (Ia) (18 patients 60%) and group (Ib) (18 patients, 60%) when compared with group Π (0 patient, 0%) (X^2 = 21.8, p< 0.001).

Table 2: Comparative and Descriptive Statistics of Clinical and Demographic Data in Each Examined Groups with the Chi-Square Test for Categorical Data and the Kruskal-Wallis Test for Non-Parametric Data.

		Groups						Test	*P-value*	Sig.
		Group (Ia) (number = 30)		Group (Ib) (number = 30)		Group Π (number = 30)				
Sex	Male	25	83%	12	40%	18	90%	X^2 = 18.7	<0.001	HS
	Female	5	17%	18	60%	2	10%			
Age (years)	Median	54.5		57.5		47		H= 5.07	0.079	NS
	IQR	42.25 –65.5		49.8-60		34.5 – 57				
HTN	Yes	15	50%	15	50%	0	0%	X^2 =16	<0.001	HS
	No	15	50%	15	50%	20	100%			
Family History	Yes	18	60%	18	60%	0	0%	X^2 = 21.8	<0.001	HS

S (significant): p-*value* < 0.05, HS (highly significant): p-*value* < 0.001, NS (non- significant) p-*value* > 0.05.
IQR: inter-quartile range H: value of Kruskal Wallis test X^2: Chi-square test.

(Table 3) contains the descriptive and comparative statistics of routine laboratory data for all groups. There is high statistically significant increased serum uric acid within group (Ib) when compared to group (Ia) and group Π (F = 33.19, p< 0.001). Serum creatinine is statistically significant increased within group (Ib) when compared to group (Ia) and group Π (F= 6.76, p= 0.002). Statistically insignificant difference among examined groups according to BUN (H=4.9, p=0.087). There is highly statistically significant increased CRP within group (Ia) when compared to group (Ib) and group Π (H= 34.4, p< 0.001). There is fairly statistically significant increased random blood sugar (RBS) within group (Ia) when compared to group (Ib) and group Π (H=6.2, p=0.046). There is highly statistically significant increased serum cholesterol in group (Ia) when compared with group (Ib) and group Π (F = 8.9, p< 0.001). A Statistically significant increased TGs in group (Ia) has been found when compared to group (Ib) and group Π (H=11.3, p= 0.004).

Table 3: Comparative and Descriptive Statistics of Routine Laboratory Data of all Participants Utilizing Kruskal Wallis test For Non-Parametric Data and ANOVA test For Parametric Data.

		Groups			Test	*P-value*	Sig.
		Group (Ia) (number = 30)	Group (Ib) (number = 30)	Group Π (number = 20)			
Uric acid (milligram per deciliters)	Mean	7.04	7.6	5.11	F = 33.19	<0.001	HS
	SD	1.2	1.11	0.84			
Creatinine (milligram per deciliters)	Mean	0.88	0.9	0.7	F=6.76	0.002	S
	SD	0.191	0.19	0.194			
BUN (mg/ dL)	Median	16	17.5	13	H= 4.9	0.087	NS
	IQR	11 – 20.5	13– 23.5	10 -16.75			
CRP (milligram per deciliters)	Median	10.1	3.3	1.2	H=34.4	<0.001	HS
	IQR	5.6 –18.6	1.1 – 5	0.4 – 1.9			
RBS (mg/ dL)	Median	165	131.5	111	H=6.2	0.046	S
	IQR	102 –212	109 – 231	93 - 144			
Cholesterol (mg/ dL)	Mean	203	197	162	F =8.9	<0.001	HS
	SD	35.4	38.3	28.4			
Triglycerides (mg/ dL)	Median	145	143	120	H=11.3	0.004	S
	*IQR	115 -200	113 -159	102 -129			

F: value of ANOVA test.

(Tables 4, 5) provide the descriptive and comparative statistics of the Genotype and Allele Frequencies of the 421G>T mutation in the ABCG2 Gene in groups I and Π. There is statistically significant increased percentage of patients with positive heterozygous GT in group (Ia) (n:7, 23%) when compared with group (Ib) (n:3, 10%) and group Π (n:2, 10%) (X^2=2.61, *p*= 0.027). The (GG) genotype demonstrated statistically insignificant difference within all studied groups (X^2=069, *p-value* = 0.71). The (G) and (T) alleles demonstrated statistically insignificant difference within all studied groups (X^2=1.18, *p-value* = 0.55).

Table 4: Descriptive and Comparative Statistics of ABCG2 Gene 421G>T Polymorphism in Patients and Controls Utilizing Chi-Square Test.

ABCG2gene poly-morphism	Groups						Test	*P-value*	Sig
	Group (Ia) (number =30)		Group (Ib) (number = 30)		Group Π (number = 20)				
Heterozygous (GT)	7	23%	3	10%	2	10%	X^2=2.61	0.027	S
Homozygous (TT)	0	0%	1	3%	0	0%	X^2=1.7	0.43	NS
Wild type (GG)	23	77%	26	87%	18	90%	X^2=069	0.71	NS

Table 5: Comparative and Descriptive Statistics of Allelic Frequencies within cases and Controls Utilizing Chi-Square Test.

Allele Frequency	Groups						Test	*P-value*	Sig
	Group (Ia) (Alleles = 60)		Group (Ib) (Alleles = 60)		Group Π (Alleles = 40)				
G	53	88%	55	92%	38	95%	X^2=1.18	0.55	NS
T	7	12%	5	8%	2	5%			

The ABCG2 gene -421 G>T mutation (rs2231142) was genotyped in all subjects. The found genotype frequencies gathered from the data and the expected genotype frequencies obtained from the Hardy-Weinberg principle were used to conduct a Chi-square test to assess the deviation from Hardy-Weinberg equilibrium (HWE). The genotype distribution demonstrated insignificant deviation from Hardy-Weinberg equilibrium between the participants (Table 6) (X^2 =1.72, p =0.18).

Table 6: Testing for the Hardy-Weinberg Equilibrium Using Chi-Square Test.

Genotype	Observed	Expected	Difference	Test	*p-value*
Wild type (GG)	71	70.3	-0.7		
Heterozygous (GT)	8	9.4	1.4	X^2=1.72	0.18
Homozygous (TT)	1	0.3	-0.7		

X^2: Chi-square test. If $P < 0.05$ - not consistent with HWE.

DISCUSSION

The ABCG2 gene is one of the genes that affect uric acid levels in blood. ABCG2 gene variants (rs2231142) are correlated with risk increasing serum uric acid in blood causing gout and hyperuricemia[11].

The ABCG2 gene is located at the long arm of human chromosome number four, region 2, band 2, sub band 1 (4q22.1). ABCG2 transporter is typically overexpressed in cell types situated at the body's entry and exit boundaries, in addition to in barrier tissues, encoded by the gene[12]. ABCG2 transporter is crucial for the excretion of uric acid at 3 distinct locations: the liver, intestine and kidney[13].

The ABCG2 gene contains frequent genetic mutations in various people. Among these mutations is 421G/T (Q141K) (rs2231142). At the 4211st position in exon 5, the thymine (T) nucleotide replaces the guanine (G) nucleotide[3]. ABCG2 gene variant (rs2231142) causes hyperuricemia and gout by decreasing expression of ABCG2 transporter on cellular membrane so decreasing uric acid excretion through kidneys and intestine[14]. The missense ABCG2 gene (rs2231142) variant is found mainly in the Central European population (about 9.4%)[15]. It varies among one percent in African and twenty-nine percent in South East Asian people[14]. Accordingly, the present research aimed to assess the function of ABCG2 gene mutation (rs2231142) in hyperuricemia and with progress of gout within Egyptian population.

The research was conducted on 80 subjects, sixty of them were divided into two subgroups, thirty Gout patients, thirty patients with hyperuricemia and twenty healthy individuals as control group. Routine laboratory tests (uric acid, triglycerides, total cholesterol, creatinine, random blood glucose and CRP) as well as RT-PCR test for ABCG2 gene mutation were done in Clinical Pathology Department, Ain Shams University Hospital for all recruited study subjects.

Studying the clinical, demographic, and routine laboratory data of the subjects revealed that risk of hyperuricemia and gout increases with age and male sex forming the majority of patients. There is increased percentage of patients with HTN in patient`s group when compared with control group in addition to elevated probability of hyperuricemia and gout within patients with positive family history. There have been associations of hyperuricemia, increased RBS, serum cholesterol and triglycerides with gout. High concentrations of CRP within gout cases have been found compared to the hyperuricemia group and control group.

The outcomes of the current research have been in agreement to the study conducted in the Mexican population where serum uric acid levels were greater in males compared to females which is in line with our study where highly statistically significant difference is discovered among examined groups according to gender[16].

Outcomes of the current research have been also in agreement to other studies[17, 18] where they found that HTN, hypertriglyceridemia and hypercholesterolemia combined with the presence of the ABCG2 rs2231142 allele improved the probability of hyperuricemia and gout which supports results of our study. There is an association between HTN, hyperuricemia, and gout, as uric acid's potential contribution to endothelial dysfunction through the induction of anti-proliferative effects on the endothelium and the impairment of nitric oxide production, which in turn induces HTN in hyperuricemic cases[17]. Regarding triglycerides and total cholesterol, it was reported that they

can cause metabolic disorders in free fatty acids, accelerate degradation of adenosine triphosphate and cause elevation of uric acid. Dyslipidemia also can stimulate the overactivity of xanthine oxidoreductase (XO) which triggers oxidative stress which in turn intensifies the dyslipidemia[18].

In the present study, the fairly statistically significant increase in RBS in gout group compared with control group was in agreement with a research that revealed significantly higher blood glucose levels in gout patients. Through the inhibition of the insulin pathway, endothelial dysfunction, and oxidative stress, hyperuricemia and gout are responsible to the various pathological mechanisms of diabetes mellitus as well as its long-term consequence[19].

Data of the current research demonstrated that high concentrations of CRP within gout cases have been found compared to the hyperuricemia group and control group which is in agreement with other researches where the former noticed that risk of gout increases with age and higher CRP concentrations have been found in hyperuricemia and gout groups compared to in normal controls[20].

Outcomes of the current research have been in agreement to the study conducted on European population where they showed that European people who carried ABCG2 variants had a significantly earlier onset of gout and hyperuricemia and the family history of gout was highly significant between them which emphasizes our study results where there is a relationship between family history and hyperuricemia and gout when compared with control group[21].

The ABCG2 gene (rs2231142) variant was genotyped in people involved in the current study. The genetic equilibrium of the people being investigated was confirmed by the application of Hardy-Weinberg law in relation to the distribution of the examined genotypes.

The current research's data indicated that the frequencies of the (G) allele and the wild type (GG) allele were greater in healthy controls than in cases. The wild type (GG) is seen in 90% in control group versus 77% in gout group and 87% in hyperuricemia group whereas the G allele is found in 95% in control group vs 88% in gout group and 92% in hyperuricemia group. Conversely, between cases with hyperuricemia and gout, the frequencies of the (T) allele, heterozygous (GT), and homozygous (TT) genotypes were significantly greater than those of healthy controls. The heterozygous (GT) is seen in 23% in gout group versus 10% in hyperuricemia group and control group. Meanwhile, the homozygous (TT) is 3% in hyperuricemia group vs 0% in gout and control group.

The present study showed that gout patients have statistically significant increased percentage of heterozygotes (GT) (23%) when compared with hyperuricemia group (10%). These results matched other results who confirmed that ABCG2 (rs2231142) mutation carried a strong risk to develop gout compared to less effects in hyperuricemia in Asians. A slight contradiction is seen in the same study but in Caucasians as a weaker risk can be expected with ABCG2 variant in gout and a stronger risk to affect serum levels of uric acid[21,22].

Outcomes of the current research were enforced by results on Chinese population, where formers confirmed associations of rs2231142 variant with hyperuricemia and gout[23]. Homozygous (TT) had 53% decreased excretion of uric acid compared to wild types. This is attributed to the presence of the (T) allele which stimulates development from hyperuricemia to gout by stimulating the immune response to MSU crystals[19].

This study carries few limitations like the small sample size which decreased the ability to detect certain correlation. Also, wholly healthy controls and cases have been chosen from the same hospital, selection bias may have influenced the outcomes.

CONCLUSION AND RECOMMENDATIONS

The ABCG2 (rs2231142) 421 G/T mutation and the progression of gout with GT genotype were found to be significantly associated in the current study. Nevertheless, it indicated the potential existence of an elevated probability of hyperuricemia and gout associated with the T allele. Additional research with a larger sample size is required to verify the correlation.

DECLARATION OF INTEREST AND FUNDING INFORMATION

The authors report no conflicts of interest.

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The authors recognize the cases and the controls for participating within this research.

CONFLICT OF INTERESTS

There is no conflicts of interest.

FINANCIAL DISCLOSURE

none.

AUTHOR CONTRIBUTION

We declare that all listed authors have made substantial contributions to all of the following three parts of the manuscript:

- Research design, or acquisition, analysis or interpretation of data.

- Drafting the paper or revising it critically.

- Approving the submitted version.

We also declare that no-one who qualifies for authorship has been excluded from the list of authors.

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دور التعدد الشكلي الجيني rs2231142 داخل ABCG2 جين بارتفاع نسبه حمض البوليك في الدم وظهور مرض النقرس في السكان المصريين

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تعتبر ناقلات ABCG2 مسؤولة عن دخول وخروج المواد المختلفه من وإلى الخلايا مثل حمض البوليك والأدوية. وهي موجودة في العديد من أنسجة الجسم مثل الكلى والأمعاء. يعد تعدد الأشكال الجيني (rs2231142) ABCG2 (Q141K) أحد الجينات المهمه والتي يقترح أنها مرتبطة بانخفاض إفراز حمض البوليك من خلال الكلى والأمعاء مما يساهم في الإصابة بفرط حمض يوريك في الدم والاصابه بمرض النقرس.

في ضوء البيانات السابقة كان الهدف من الدراسة الحالية هو دراسة العلاقة بين تعدد أشكال 421G>T لجين ABCG2 ووجود زياده في حمض البوليك في الدم والاصابه بالنقرس.

كشفت الدراسة الحالية أن النمط الجيني (GG) ومعدلات الأليل (G) كانت أعلى في الأصحاء مقارنة بالمرضى. وفي الوقت نفسه، كانت معدلات التراكيب الوراثية (GT) و (TT) وكذلك الأليل (T) أعلى بين المرضى مقارنة مع الأصحاء.

في الختام، أظهرت الدراسة الحالية وجود ارتباط كبير بين تعدد الأشكال ABCG2 (rs2231142) وظهورمرض النقرس خاصة مع النمط الجيني GT. ومع ذلك، فقد أشارت الدراسه إلى احتمال وجود خطر كبير للإصابة بالنقرس وزياده حمض البوليك في الدم مع أليل T