Polymorphism of ADAMTS-13 gene rs28503257 in Iraqipatients with Hypertension

Suhad Mohammad Hamed[1], Prof. Dr. Zafir Hassan Ghali[1]

[1]Departmen of Biology –College of Education for pure Sciences-University of Wasit –Iraq

KEYWORDS

Polymorphism, ADAMTS-13 gene

ABSTRACT

The aim of this study was to investigate the association of polymorphism of ADAMTS-13 gene to the susceptibility of hypertension in patients with hypertension in an Iraqi population. Forty-five hypertensive patients (23 males and 22 females), their age 40-70 years and 35 healthy controls (18 males and 17 females), their age range between 40-70 years. were selected from Wasit Province using a convenient sampling method. Genetic polymorphism of ADAMTS13) rs28503257 A/G was carried out using TaqMan -PCR. In patients and controls, the genotypic and allelic distributions of adisentgrine and metallopeptedase with a thrombospondin type1 motife13(ADAMTS13) rs28503257 A/G of the study populations were consistent with Hardy-Weinberg equilibrium. The genotypes frequecies of ADAMTS-13 rs 28503257 A/G of patients with hypertension manifested non-significant differences when compared with healthy control group AA =40(89%), AG =5(11) in patients vs. 30(86), 5(14) P=0.67 in controls for each genotype respectively. There were no hypertensive patients or controls carrying the genotype GG in the study sample. The A and G allele frequencies in SNP rs28503257 A/G were not significantly different between the two groups (P>0.05). The A allele was the major one in studied groups with a percent of (0.9286) and (0.9444) in control and patients groups respectively. Whereas the A allele was the minor one with a percent of (0.0714) and (0.0556) in these groups respectively. The association analysis revealed that individuals carrying the homozygous AA genotype were assocaited with hypertension OR=1.3333 (CI95% 0.3537 to 5.0259) and P= 0.6709 indicating that a positive association with the disease.However,the individuals with a hetrozygous AG genotype showed negative association with the disease OR= 0.7500 (CI95% 0.1990 to 2.8271) ,P=0.6709. Although no individuals carrying the genotype GG were observed in patients and controls, the odds ratio can be calculated in the presence of other genotypes OR= 0.7802 (CI95% 0.0151 to 40.2986), P= 0. 9019.These results suggest that the A allele may be considered as a risk allele in hypertension whereas the G allele is a protective allele agianst hypertension. The genetic model for ADAMTS-13 in comparison between hypertensive patients and controls .The dominant model indicated that patients of(AG+GG/AA) genotypes decreased the association with hypertension comparing with control with OR=1.333 CI95%0.3537 to 5.025: patients (40/5 and 0.00) in patients vs.(30/5 and 0.00) with OR== 0.7500(CI95%0.1990 to 2.8271) , P =0.6709,P=0.6709.The recessive model revealed that patients carrier the genotype(AA+AG/GG) increased the association with the disease (0.0/40 and 5) in patients compared with controls(0.00/30 and 5) with OR=1.2817(CI95% 0.0248 to 66.199), P=0. 9019.The Over dominant model revealed that patients carrier the genotype (AA+GG/AG) increased the association with the disease (0.040 and 5) in patients compared with controls (0.00/30 and 5) with OR=1.3333(CI95%0.3537 to5.0259),P=0.6709. In coclusion, the polymorphisms ADAMTS-13 rs28503257 variant A/G with are associated with the susceptibility of hypertension

1. Introduction

Hypertension is a major risk factor for cardiovascular diseases, affecting millions of individuals worldwide. The pathogenesis of hypertension involves complex interactions between genetic and environmental factors. In recent years, research has focused on identifying genetic variants associated with hypertension susceptibility and severity. One gene that has gained attention in this context is ADAMTS13, which encodes a metalloproteinase responsible for cleaving von Willebrand factor (VWF), a key player in platelet adhesion and aggregation. One of the primary objectives is to elucidate the role of genetic variants in the ADAMTS-13 gene in the development and progression of hypertension. By identifying specific polymorphisms associated with hypertension, researchers can better understand the hereditary components that predispose individuals to this condition (Wang et al.,2020). ADAMTS-13 polymorphisms may influence vascular health and blood pressure regulation. ADAMTS-13 is involved in the cleavage of von Willebrand factor (VWF), which plays a crucial role in platelet aggregation and vascular homeostasis. Dysregulation of this pathway can contribute to thrombotic events and vascular complications associated with hypertension. Understanding these mechanisms can provide insights into how genetic variations affect disease processes (European Respirotry Journal.2019 ; Wang et al.,2020).

The identification of specific ADAMTS-13 gene polymorphisms associated with hypertension could lead to the development of genetic biomarkers for risk stratification. This would enable healthcare providers to identify individuals at higher risk for hypertension and its complications, allowing for earlier intervention and personalized treatment strategies.

The investigation of ADAMTS-13 gene polymorphisms in hypertension is aimed at uncovering the genetic basis of this condition, understanding its pathophysiological mechanisms, identifying potential biomarkers for risk assessment, and exploring their associations with clinical outcomes. Such research is essential for advancing personalized medicine approaches in the management of hypertension. The current study aims to investigate the association of polymorphism of ADAMTS-13 gene to the susceptibility of hypertension.

2. Methodology

This is a case –control study, The participants included 45 of type2 diabetes mellitus patient (23 males and 22 females) their age 40 to 70 years (mean ± standard deviation: 51.92 ± 51.50 years, median= 51 years). The control group comprised of 35 healthy individuals (18 males and 17 females), their age 40-70 years (mean ± standard deviation: 51.52 ± 47.18 years, median=48 years). Data collection encompassed a range of factors, including demographic details, medical history, and sample collection date, gathered from participants who met global diagnostic criteria. samples were collected from Al-Zahra'a Teaching Hospital and blood bank in Kut, Iraq,For blood sample collection, 3 ml of blood was obtained via vein puncture from each participant, with the collected blood then transferred to sterile ethylenediaminetetraacetic acid –k3 (EDTA) tubes, labelled, and stored at -20°C for subsequent DNA extraction and genotyping.

Genomic DNA Extraction

Genomic DNA was extracted from whole blood utilizing the Quick-DNA™ Blood MiniPrep kit (Zymo, USA) Catalogue Nos. D3072 & D3073. The quality of the extracted genomic DNA was assessed via Nanodrop, measuring the A260/A280 absorbance ratio within the range of 1.8 to 2.0, indicative of high quality.

SNPs Genotyping:

The TaqMan custom SNP genotyping assay from Thermo Fisher Scientific was utilized for genotyping the SNP rs28503257 in the a metallopeptidase with thrombospondin type 1 motif 13 (ADAMTS-13). Real-time PCR was employed for the allele-specific discriminating approach. The reference and alternative

alleles for rs28503257 were referred to from NCBI.

Statistical Analysis:

The results of the serum were presedent as mean + standard error and significant differences were analyzed by ANOVA analysis the genotype and allele frequencies for SNPs were calculated directly counting method. Hardy_Weinberg Equilibrium (HWE)for each SNP was investigated statistically significant when les than 0.05

3. Result and Discussion

Genotypes and allele frequencies of A disintegrin and metallopeptedase with a thrombospondin type 1 motif 13 (ADAMTS-13) rs28503257 in hypertensive patients and controls

Forty-five hypertension patients (23 males and 22 females) and 35 healthy controls (18 males and 17 females) were genotyped for of adisentegrine and metallopeptedase with a thrombospondin type1 motife13(ADAMTS-13). In patients and controls, the genotypic and allelic distributions of adisentgrine and metallopeptedase with a thrombospondin type1 motife13(ADAMTS13) rs28503257 A/G of the study populations were in Hardy–Weinberg equilibrium adisentgrine and metallopeptedase with a thrombospondin type1 motife13(ADAMTS-13) rs28503257 A/G was consistent with Hardy-

Weinberg equilibrium

X2 =0.1814,P=0.67016; X2 =0.1693,P=0.68 respectively. These results indicate that the frequency of each gene has reached genetic equilibrium and the selected samples were representative of the population. The allele and genotype frequencies of ADAMTS-13 gene polymorphisms were used to estimate the odds ratio (OR), confidence intervals (95% CIs) and P-value. The genotypes frequecies of ADAMTS-13 rs 28503257 A/G of patients with hypertension manifested non-significant differences when compared with healthy control group AA =40(89%), AG =5(11) in patients vs. 30(86), 5(14) P=0.67 in controls for each genotype respectively. There were no hypertensive patients or controls carrying the genotype GG in the study sample. The A and G allele frequencies in SNP rs28503257 A/G were not significantly different between the two groups (P>0.05). The A allele was the major one in studied groups with a percent of (0.9286) and (0.9444) in control and patients groups respectively. Whereas the A allele was the minor one with a percent of (0.0714) and (0.0556) in these groups respectively.

Table 3.1: Distribution of genotypes and allele frequencies of ADAMTS-13 rs28503257 A/G in patients with hypertension and healthy controls

Groups	**Genotype No (%)**			**Allele Frequency No (%)**	
	AA	**A G**	**GG**	**A**	G
Control	30(86)	5(14)	0.00	65(0.9286)	5(0.0714)
Patients	40(89)	5(11)	0.00	85 (0.9444)	5(0.0556)
Chi Square (X^2)	**0.1814**			0.1693 0.68	
P-value	**0.67**				
Significance Level	**NS**				

Susceptibility analysis of Adisentegrin and Mataloopeptedase with thormospondine type1 motife13 rs28503257 (ADAMTS-13) to hypertension

Table (3.2) shows the association of each genotype of (ADAMTS-13)with susceptibility to hypertension. : The association analysis revealed that individuals carrying the homozygous AA genotype were assocaited with hypertension OR=1.3333 (CI95% 0.3537 to 5.0259) and P= 0.6709 indicating that a positive association with the disease.However,the individuals with a hetrozygous AG genotype showed negative association with the disease OR= 0.7500 (CI95% 0.1990 to 2.8271) ,P=0.6709. Although no individuals carrying the genotype GG were observed in patients and controls, the odds ratio can be calculated in the presence of other genotypes OR= 0.7802 (CI95% 0.0151 to 40.2986), P= 0.9019.These results suggest that the A allele may be considered as a risk allele in hypertension whereas the G allele is a protective allele agianst hypertension.

Table 3.2 Odds ratio(95%confident intervals)for hypertension in relation to ADAMTS-13 genotypes

Genotypes	**Control**	**Patients**	**OR**	**OR95%CI**	***P*-value**	**Significance level**
AA	30	40	1.3333	0.3537 to 5.0259	0.6709	Ns.
AG	5	5	0.7500	0.1990 to 2.8271	0.6709	Ns.
GG	0.00	0.00	**0.7802**	0.0151 to 40.2986	0.9019	Ns.

Ns.non-significant P>0.05

Genetic model for (ADAMTS-13) rs28503257 A/G polymorphisms in patients with hypertension compared with Controls

Table (3.5) represented the genetic model for ADAMTS-13 in comparison between hypertensive patients and controls .The dominant model indicated that patients of(AG+GG/AA) genotypes decreased the association with hypertension comparing with control with OR=1.333 CI95%0.3537 to 5.025: patients (40/5 and 0.00) in patients vs.(30/5 and 0.00) with OR== 0.7500(CI95%0.1990 to 2.8271) , P =0.6709.9,P=0.6709.The recessive model revealed that patients carrier the genotype(AA+AG/GG) increased the association with the disease (0.0/40 and 5) in patients compared with controls(0.00/30 and 5) with OR=1.2817(CI95% 0.0248 to 66.199), P=0. 9019.The Over dominant model revealed that patients carrier the genotype(AA+GG/AG) increased the association with the disease (0.040 and 5) in patients compared with controls (0.00/30 and 5) with OR=1.3333(CI95%0.3537 to5.0259),P=0.6709.

Table 3.3 Calculation of genetic model of ADAMTS-13 polymorphisms in hypertensive patients compared with controls

Genetic model	Genotype	Controls	Patients	OR	OR95%CI	*P* value	Significance level
Dominant	**AG+GG AA(Ref.)**	**5/0.00 30**	**5/0.00 40**	0.7500	0.1990 to 2.8271	0.6709	**Ns.**
Recessive	**AA+AG GG(Ref.)**	**30/5 0.00**	**40/5 0.00**	1.2817	0.0248 to 66.1996	0.9019	**Ns.**
Over-dominant	**AA+GG AG(Ref.)**	**30/0.00 5**	**40/0.00 5**	1.3333	0.3537 to 5.0259	0.6709	**Ns.**

Ns:non-significant. P>0.05

Discussion

The of adisentgrine and metallopeptedase with a thrombospondin type1 motife13(ADAMTS-13) enzyme is involved in controlling the size and activity of von Willebrand factor, which affects platelet aggregation and thrombus formation.This single nucleotide polymorphism (SNP) in the ADAMTS-13 gene can lead to variations in the enzyme's activity or stability, which might influence the risk of developing conditions associated with abnormal blood clotting.It has been hypothesized that genetic predisposition to hypertension may be associated with variations in a single gene. Within a gene, a single nucleotide polymorphism (SNP) or a combination of SNPs that inherit together (haplotype) can be studied.The current study investigated the possible association of the individual SNP (rs28503257 A/G) and the with the risk of hypertension. As a main disease affecting human health in modern society, hypertension is mainly caused by such factors as diet, lifestyle, environmental factors, genetic characteristics, and immune homeostasis)ren et al.,2018).

In previous studies that have investigated the association of polymorphisms of several factors among patients with type2 DM from Wasit province, Bilal and Ghali,2021 revealed that IL-10 is a major contributor to the onset of type 2 diabetes mellitus and there may be a correlation between low levels of interleukin-10 and type two diabetes. (Al-Sarray and Ahmed ,2021) found that may be a correlation between high levels of TNF-α and type 2 diabetes mellitus .)Shamkhi and Ahmed, 2021(displayed that levels of SIRT1 may be not associated with type2 diabetes mellitus.Furthermore, the cell free mitochondrial DNA increases significantly in patients with type2 diabetes mellitus(Hussein and Ghali,2022). COX-1 is a major contributor to the onset of type 2 diabetes and there may be an association between low levels of cyclooxygenase-1and type 2 diabetes(Jebil and Ghali2021). The association analysis of IL-17AG197A gene polymorphism with T2DM displayed that heterozygous AG genotype of IL-17AG197A showed a risk association among T2DM with OR=1.24 CI95% (0.31 - 5.01) p-value =1.00 and the G allele was associated with an increased risk ofT2DM)Khadhum and Ahmed ,2022).)Mahmood and Ghali,2022a(revealed that there was an association between the polymorphism of Osteoprotegerin (OPG) polymorphism and susceptibility to type2 diabetes mellitus.)Mahmood and Ghali,2022 b(found also that there may be a correlation between high levels of OPG and T2DM.)Thamer et al.,2020(found that IL-4 concentrations had a non-significant difference when compared patients with type-2 diabetes mellitus with the control while patients with T2DM revealed

elevated serum levels of IL-6 compared to control group.)Ahmed and Ghali,2019(found that different transversion and transition mutations at IL-6-174 (G/C) gene are associated with type-2 diabetes mellitus.)Alwan and Ghali,2023a(revealed that The polymorphism of telomerase reverse transcriptase(TERT) rs 2736100 variant A <C are associated with the susceptibility of type2 diabetes mellitus. The association analysis of (TERT) rs2853669 with susceptibility to type2 diabetes mellitus showed that the individuals carrying the heterozygous AG genotype and homozygous AA genotypes were more likely to have a significantly increased risk of type2 diabetes mellitus(Alwan and Ghali,2023 b).The human insulin

receptor gene rs1366600 has possible roles in type2 diabetes mellitus susceptibility (Foad and Ahmed ,2023a). A SNPs located within miRNA-binding sites:acyl-CoA synthetase 1 rs2292899 have possible roles in type2 diabetes mellitus susceptibility. (Foad and Ahmed ,2023 b) The homozygous GG genotype of acyl-CoA synthetase 1 rs2292899 is associated with type2 DM.(Iqbal and Zafir,2022) revealed that renalase serum levels were markedly higher in hypertensive patients although there was an insignificant difference (72.2±12.6), controls (65.40±8.91), P= 0.071. Tuama and Ghali,2022 also demonstrated that the renalase rs2296545 GG genotype and G allele could be a risk factor for hypertensive patients. (Iqbal, & Zafir,2022). Association of renalase genotypes with their serum levels in Iraqi hypertensive patients.

The genotypic and allelic distributions of adisentgrine and metallopeptedase with a thrombospondin type1 motife13(ADAMTS-13) rs28503257 A/G of the study populations were in Hardy–Weinberg equilibrium. These results indicate that the frequency of each gene has reached genetic equilibrium and the selected samples were representative of the population. The genotypes frequencies of ADAMTS-13 rs 28503257 A/G of patients with hypertension manifested non-significant differences when compared with healthy control group. The A and G allele frequencies in SNP rs28503257 A/G were not significantly different between the two groups. The association analysis revealed that individuals carrying the homozygous AA genotype were associated with hypertension indicating that a positive association with the disease.However,the individuals with a heterozygous AG genotype showed negative association with the disease .These results suggest that the A allele may be considered as a risk allele in hypertension whereas the G allele is a protective allele against hypertension. The above results suggest that there is a correlation between the development of hypertension and ADAMTS-13 gene polymorphism, and hypertensive patients with A allele and the genotype AA of rs 28503257 locus are more prone to hypertension, while those GA and GG genotypes are less likely to suffer from hypertension.

The genetic model for ADAMTS-13 in comparison between hypertensive patients and controls revealed that the dominant model indicated that patients of(AG+GG/AA) genotypes decreased the association with hypertension comparing with control .The recessive model revealed that patients carrier the genotype(AA+AG/GG) increased the association with the disease in patients compared with controls.The Over dominant model revealed that patients carrier the genotype(AA+GG/AG) increased the association with the disease in patients compared with controls.These results are consistent with (Wang et al.,2020) who explored the relationships between ADAMTS-13 gene polymorphisms and hypertension-induced atrial fibrillation in Chinese population. Research has explored the relationship between ADAMTS-13 polymorphisms and hypertension, but results can be mixed. Some studies may suggest a correlation between specific ADAMTS-13 gene variants and increased risk of hypertension, while others might not find a significant association.

Three ADAMTS-13 polymorphisms: C1342G (Q448E), C1852G (P618A) and C2699T (A900V) in a group of 560 patients with cardiovascular disease were investigated by (Schettert et al.,2010).They observed a significant association between ADAMTS-13 900V variant and an increased risk of death (OR: 1,92 CI: 1,14-3,23, p = 0,015) or death from cardiac cause (OR:2,67, CI: 1,59-4,49, p = 0,0009). No association between events and ADAMTS-13 Q448E or P618A was observed.

More than 76 mutations of ADAMTS13 are reported in the literature. Missense mutations, which

constitute nearly 60% of ADAMTS-13 mutations, preferentially localize in the 5'-half of the gene encoding the N-terminal half of the protein, where the domains that are indispensable for ADAMTS-13 catalytic function are situated (Lotta et al.,2010).

The proline (Pro) to serine (Ser) polymorphism in codon 475 of the ADAMTS-13 gene has been identified. This Pro475Ser polymorphism, caused by a base substitution of C1423 to T in exon 12, is reported to impair the activity of ADAMTS-13. In a Japanese study the frequency of the rare 475Ser allele of this single nucleotide polymorphism (SNP) was 5.1% in 364 healthy controls and it has been suggested that the 475Ser allele may increase the risk of arterial thrombosis because of the reduced activity of ADAMTS-13 (Sadler.,2002; kokame et al.,2002).

Hanson et al.investigated 6 SNPs of the ADAMTS-13 gene in patients with ischemic stroke. Three minor alleles of these SNPs showed an association with ischemic stroke. One minor allele of these SNPs (rs4962153) showed an increase in risk OR 1.25 (95% CI 1.01–1.54), while the other two minor alleles of rs2285489 and rs2301612 had a decreased risk of ischemic stroke; OR 0.82 (95% CI 0.70–0.97) and OR 0.85 (95% CI 0.73–1.00) respectively (Hanson et al.,2009).

Mutations in the ADAMTS-13 gene can lead to an ADAMTS-13 enzyme deficiency, which is related to Upshaw–Schulman syndrome (USS). USS is a common type of thrombotic thrombocytopenic purpura (TTP). 29 ADAMTS-13 pathogenic mutations detected in 24 TTP patients, the missense mutations (55%) are the most common type of mutation, followed by frameshift mutations (28%). Exons contained more mutations than introns. 11 patients (45.8%) showed the course of chronic relapsing TTP. 13 patients (54.2%) responded to plasma infusion. Nine patients (37.5%) had a history of hemolysis (Li et al.,2021).

Gene polymorphism, one of the most important factors affecting the physiological process of the body and the pathological process of diseases, greatly influences the susceptibility of many diseases including malaria (Nardini et al.,2019) and asthma (Dutta et al.,2017). Besides, the development and procession of hypertension are associated with some gene polymorphisms, such as CYP4F2 rs2108622 polymorphism (Luo et al.,2018), PPAR-γ2 Pro12Ala polymorphism (Yang et al.,2018), and ACE2 gene polymorphism (Fan et al.,2019).ADAMTS-13, an important gene influencing coagulation function and thrombosis,may affect the development of hypertension.

ADAMTS-13 is amember of the thrombospondin integrin metallopeptidase family and vWF-CP synthesized by stellate cells, which has a relation to thrombotic microangiopathy,disseminated intravascular coagulation, and inflammatory

diseases (Obermeier et al.,2019; Kantneni et al.,2019). Moreover, it is reported that ADAMTS-13 can affect the development of cardiovascular diseases, like myocardial infarction and unstable angina pectoris (Schooling et al.,2018). It follows that ADAMTS-13 may be an important participant in the regulation on cardiovascular diseases. Besides, ADAMTS-13 gene polymorphism has been reported to affect the pathological process of various diseases, including cerebral aneurysm (arning et al.,2016).

Wang et al.,2020 found that a correlation between the development of hypertension- induced AF and ADAMTS-13 gene polymorphism, and hypertensive patients with T allele of rs3094374 locus, T allele of rs34054981locus, and the genotype CT of rs34054981 are more prone to AF, while those with rs28503257 GA genotype are less likely to suffer AF. Furthermore, there was an association between ADAMTS-13 rs34054981 polymorphism and the expression of ADAMTS-13 gene ($p<0.05$), and the expression of ADAMTS-13 gene was lowered

in patients with TT genotype in AF group, suggesting that the effects of ADAMTS-13 gene polymorphism on the susceptibility and progressionof hypertension-induced AF may be achieved by regulating the expression of ADAMTS-13gene (Wang et al.,2020).

4. Conclusion and future scope

Accodring to the resuts pf the present study,the following conclusions can be deduced:

The polymorphisms ADAMTS-13 rs28503257 variant A/G with are associated with the susceptibility of hypertension. The genotype AA of ADAMTS-13 rs28503257 variant A/G increases the risk of hypertension and the A allele is a risk factor in hypertension.Wherese,the genotypes AG and GG decrease the risk of the disease .The A allele of ADAMTS-13 rs28503257 variant A/G may be considered as a risk allele in hypertension whereas the G allele is a protective allele against hypertension.

The Over dominance and recessiveness in the alleles of ADAMTS-13 rs28503257 variant A/G increases the association with hypertension. The dominance in the alleles of ADAMTS-13 rs28503257 variant A/G decreases the association with hypertension

Reference

[1] Ahmed, I.H. and Ghali, Z.H., 2019. Transversion and transition mutations of interleukin-6 gene-174 (G/C) in patients with type-2 diabetes mellitus. Gene Reports, 17, p.100478.

[2] Al-Sarray, A.J. and Ahmed, I.H., 2021. Serum TNF-A Concentrations In Type Two Diabetes Mellitus. nveo-natural volatiles & essential oils journal| nveo, pp.540-546.

[3] Alwan, M.A., 2023. polymorphism of Telomerase reverse transcriptase (TERT) gene rs2736100 in iraqi patients with type2 diabetes mellitus. journal of healthcare and life-science research, 2(9), pp.71-79.

[4] Alwan, M.A., 2023. polymorphism of Telomerase reverse transcriptase (TERT) gene rs2736100 in iraqi patients with type2 diabetes mellitus. journal of healthcare and life-science research, 2(9), pp.71-79.

[5] Arning, A., Jeibmann, A., Köhnemann, S., Brokinkel, B., Ewelt, C., Berger, K., Wellmann, J., Nowak-Göttl, U., Stummer, W., Stoll, M. and Holling, M., 2016. ADAMTS genes and the risk of cerebral aneurysm. Journal of neurosurgery, 125(2), pp.269-274.

[6] Dutta, S., Mondal, P., Saha, N.C., Moitra, S., Podder, S., Ghosh, A. and Saha, G.K., 2017. Role of offending out-door aero-allergen and CD14 C (-159) T polymorphism in development and severity of asthma in a Kolkata patient population. African Health Sciences, 17(4), pp.1101-1109.

[7] Enooku, Kenichiro, Reiko Kato, Hitoshi Ikeda, Makoto Kurano, Yukio Kume, Haruhiko Yoshida, Tomoko Ono et al. "Inverse correlations between serum ADAMTS13 levels and systolic blood pressure, pulse pressure, and serum C-reactive protein levels observed at a general health examination in a Japanese population: a cross-sectional study." Clinica chimica acta 421 (2013): 147-151.

[8] Fan, Z., Wu, G., Yue, M., Ye, J., Chen, Y., Xu, B., Shu, Z., Zhu, J., Lu, N. and Tan, X., 2019. Hypertension and hypertensive left ventricular hypertrophy are associated with ACE2 genetic polymorphism. Life sciences, 225, pp.39-45.

[9] Foad, M.H. and Ahmed, I.H., 2023. Polymorphism of acyl-CoA synthetase 1 ACSL1 Gene rs2292899 in Iraqi Patients with type2 Diabetes Mellitus. JCHR, 13(5), pp.2251-6727.

[10] Foad, M.H. and Ahmed, I.H., 2023. Polymorphism of Human Insulin Receptor INSR Gene Rs1366600 in Iraqi Patients with type2 Diabetes Mellitus. Central Asian Journal of Medical and Natural Science, 4(5), pp.226-232.

[11] Ghali, H.D.J.Z.H., 2021. Evaluation Of Serum Levels Of Cyclooxygenase-1 (COX-1) Among Patients With Type Two Diabetes Mellitus (T2DM). nveo-natural volatiles & essential oils journal| nveo, pp.511-515.

[12] Hanson, E., Jood, K., Nilsson, S., Blomstrand, C. and Jern, C., 2009. Association between genetic variation at the ADAMTS13 locus and ischemic stroke. Journal of Thrombosis and Haemostasis, 7(12), pp.2147-2149.

[13] Hussein, A.R. and Ghali, Z.H., 2022. Analysis Of Cell Free DNA And Cf-Mt DNA As Molecular Markers In Patients With Type-2 Diabetes Mellitus. nveo-natural volatiles & essential oils journal| nveo, pp.444-449.

[14] Kadhum, M.S. and Ahmed, I.H., 2022. The influence of IL-17A genetic polymorphism on the susceptibility of Type 2 diabetes mellitus in Iraqi patients. Chinese Journal of Medical Genetics, 31(3), pp.288-291.

[15] Katneni, U.K., Ibla, J.C., Hunt, R., Schiller, T. and Kimchi-Sarfaty, C., 2019. von Willebrand factor/ADAMTS-13

interactions at birth: implications for thrombosis in the neonatal period. Journal of Thrombosis and Haemostasis, 17(3), pp.429-440.

[16] Kokame, K., Matsumoto, M., Soejima, K., Yagi, H., Ishizashi, H., Funato, M., Tamai, H., Konno, M., Kamide, K., Kawano, Y. and Miyata, T., 2002. Mutations and common polymorphisms in ADAMTS13 gene responsible for von Willebrand factor-cleaving protease activity. Proceedings of the National Academy of Sciences, 99(18), pp.11902-11907.

[17] Li, P., Jiang, J., Xi, Q. and Yang, Z., 2021. An ADAMTS13 mutation that causes hereditary thrombotic thrombocytopenic purpura: a case report and literature review. BMC Medical Genomics, 14, pp.1-9.

[18] Lotta, L.A., Garagiola, I., Palla, R., Cairo, A. and Peyvandi, F., 2010. ADAMTS13 mutations and polymorphisms in congenital thrombotic thrombocytopenic purpura. Human mutation, 31(1), pp.11-19.

[19] Luo, X.H., Li, G.R. and Li, H.Y., 2015. Association of the CYP4F2 rs2108622 genetic polymorphism with hypertension: a meta-analysis. Genet Mol Res, 14(4), pp.15133-15139.

[20] Mahmood, D.Q. and Ghali, Z.H., 2022. association of osteoprotegerin opg t950c polymorphism to susceptibility of type 2 diabetes mellitus.

[21] Nardini, L., Holm, I., Pain, A., Bischoff, E., Gohl, D.M., Zongo, S., Guelbeogo, W.M., Sagnon, N.F., Vernick, K.D. and Riehle, M.M., 2019. Influence of genetic polymorphism on transcriptional enhancer activity in the malaria vector Anopheles coluzzii. Scientific reports, 9(1), p.15275.

[22] Newnham, M., South, K., Bleda, M., Auger, W.R., Barberà, J.A., Bogaard, H., Bunclark, K., Cannon, J.E., Delcroix, M., Hadinnapola, C. and Howard, L.S., 2019. The ADAMTS13–VWF axis is dysregulated in chronic thromboembolic pulmonary hypertension. European Respiratory Journal, 53(3).

[23] Obermeier, H.L., Riedl, J., Ay, C., Koder, S., Quehenberger, P., Bartsch, R., Kaider, A., Zielinski, C.C. and Pabinger, I., 2019. The role of ADAMTS-13 and von Willebrand factor in cancer patients: results from the Vienna cancer and thrombosis study. Research and Practice in Thrombosis and Haemostasis, 3(3), pp.503-514.

[24] Ren, L.Q., Sun, X.X. and Guan, Y., 2018. Effects of sevoflurane or propofol combined with remifentanil anesthesia on clinical efficacy and stress response in pregnant women with pregnancy-induced hypertension. European Review for Medical & Pharmacological Sciences, 22(6).

[25] Sadler, J.E., 2002. A new name in thrombosis, ADAMTS13. Proceedings of the National Academy of Sciences, 99(18), pp.11552-11554.

[26] Schettert, I.T., Pereira, A.C., Lopes, N.H., Hueb, W.A. and Krieger, J.E., 2010. Association between ADAMTS13 polymorphisms and risk of cardiovascular events in chronic coronary disease. Thrombosis research, 125(1), pp.61-66.

[27] Schooling, C.M., Luo, S. and Johnson, G., 2018. ADAMTS-13 activity and ischemic heart disease: a mendelian randomization study. Journal of Thrombosis and Haemostasis, 16(11), pp.2270-2275.

[28] Shamkhi, R.J. and Ahmed, I.H., 2021. Association between Sirtuin1 levels and Type2-Diabetes Mellitus. Turkish Journal of Physiotherapy and Rehabilitation, 32, p.3.

[29] Thamer, M.M., Wong, C.F. and Ghali, Z.H., 2021. Estimation of Interleukin-4 (IL-4) and Interleukin-6 (IL-6) Levels in Sera From Patients with Type 2 Diabetes Mellitus. Indian Journal of Forensic Medicine & Toxicology, 15(1).

[30] Tuama, I.S. and Ghali, Z.H., Association of Renalase rs2296545 gene polymorphism to susceptibility of hypertension in Iraqi patients.

[31] Wang, H.J., Xiao, M., Zeng, Z., Bao, D. and Fan, L.L., 2020. Correlation analysis between ADAMTS-13 gene polymorphism and hypertension-induced atrial fibrillation. European Review for Medical & Pharmacological Sciences, 24(5).

[32] Yousif, B.A. and Ghali, Z.H., 2021. Evaluation Of Serum Levels Of Interleukin-10 Among Patients With Type Two Diabetes Mellitus (T2DM). nveo-natural volatiles & essential oils journal| nveo, pp.496-499.