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A CROSS-SECTIONAL RESEARCH ON THE WEAK ASSOCIATION OF SERENE THREONINE KINASE – 39 GENE TO ESSENTIAL HYPERTENSION (EHTN) WITH RESPECT TO INCREASING AGE FACTOR, BMI AND DIABETES IN THE ABSENCE OF EXERCISE AND PHYSICAL ACTIVITY

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Abstract:
Objective: *This research was aimed to study the (Serine Threonine Kinase-39) A-G prevalence polymorphism in the population that is settled in the rural areas.*
Methods: *Nature of the research was cross-sectional, random which was completed in the time span of 2015 – 2017 on 528 participants. We excluded secondary hypertension cases from the record of this research. Controls and cases were respectively Normotensives and Hypertensives. We performed genotyping by tetra-primer amplification refraction mutation system by using a chain reaction of the polymerase and analysis of the data was carried out on SPSS.*
Results: *Serine Threonine Kinase – 39 has an association with the critical hypertension which was measured as (3.07) (CI 95%, range 2.10 – 4.49) and in units it was described as (mmHg) / G allele (P-Value = 0.001). An elevated systolic BP (Above 140 mmHg) which reflected (0.76) (CI, 95%, 0.47 – 1.23) (P – value= 0.235) & raised diastolic Blood Pressure (> 90 mmHg) reflected as 0.93 (95% CI, 0.61 – 1.44) units/mmHg / G allele (P-value = 0.735). Risk allele G frequency was under (33.3%) in comparison to the allele – A (66.7%), (P-Value = 0.0001). Non-significant genetic factors size was observed as (0.062, P-value = 0.153), GG homozygotes (- 0.013, P-value = 0.772) and for the AG heterozygotes. Risk factors effective size was observed as (age above 50 years, diabetes and BMI above 23) had an association with the incidence of essential hypertension (0.747, P-value = 0.000). Effect was increased by (12.04 fold) in GG genotype and another three folds with the influence of the factors of risk which was required for the single allele-G in AG heterozygotes cases.*
Conclusion: *Risk of the essential hypertension as observed by polymorphism as observed in our research was not same as it was reported previously by a European author. It was suggested that variant G allele has a weak association when the environmental risk factors are absent.*
Keywords: *Single nucleotide polymorphism (STK – 39) (rs35929607), Serine-threonine kinase-39 (STK39) gene, Cardiovascular diseases, Essential hypertension, Risk Factor size effect, STK – 39 Genotypes and Pakistani population.*

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INTRODUCTION:

There is an association of the cardiovascular diseases and essential hypertension with step-by-step increasing rate of mortality and morbidity in the world as it was reported back in 2000 as (26.4%) [1, 2]. The increase in this incidence is expected to rise by 2025 up to sixty percent [2]. Hypertension causes 7.1 million deaths in the world every year [3]. Wang is of the view that (SNP rs35929607) in Serine Threonine Kinase – 39 (STK 39) gene has an association with elevated BP [5]. Location of the (SNP rs35929607) is in intronic gene area. It is graded that (SNP consistent with rs35929607) is either better surrogate or itself a functional variant [5]. We aimed at the stud of the (SNP rs35929607) prevalence, allele frequencies and genotypes to perform an analysis about the risk factors size in the population of Pakistan.

According to the Biotechnology center, STK39 comprises of eighteen exons and it covers a region of 293.65 kilo base which is in the range of (168812426 – 168518776) on reverse gene strand [36]. BP is influenced by the allocation of chromosome of (STK 39) at (2q24.3). STK – 39 variants human gene are responsible for the production of proteins also influences BP with the increase in the expression of STK – 39 and as a result it alters the excretion of renal sodium. On a platform (Affymetrix 100K), a number of SNPs were settled within (5 kb of STK 39) [5]. STK response is encoded in this gene for renal tubular cell low sodium state or hypotonicity state also called as the cellular-stress. It causes the production of the cation chloride phosphorylation which is coupled with the cotransporters that activate p38 which is a Mitogen activated protein (MAP) in the pathway of kinase pathway. Sodium is absorbed in this phenomenon and water increases the BP and intravascular volume [6 – 9]. G allele presence of (rs35929607) also increases the downstream sodium potassium chloride co-transporter (NKCC2) activity and sodium chloride cotransporter (NCC), which promotes Na+ reabsorption, BP and intravascular volume is increased [5].

In the numerous essential hypertension related genes, few are of prime importance to regularize the mechanism of BP. For instance, RENIN, gene of angiotensin converting enzyme (ACE), gene of angiotensin – II receptor – I (AGTR – I) and lipid regulation feedback loops gene such as apolipoprotein A – 1 (APOA – 1). There is a need in the future research studies that focus is to be given to the genetic polymorphisms definite number which contribute in the genetic variation that depends on environmental and genetic effects [4]. Therefore, genetic reaction in various genes is reflected through SNPs which constitutes on the very basic clarification instrument of loop of feedback that is operated to enhance the level of BP.

Hypertension, atherosclerosis and type-2 diabetes mellitus (T2DM) are well known polygenic based complicated disorders [10]. Dyslipidemia cluster and Hypertension are repeated in the category of CVD [11]. Higher prevalence has been reported in the population of US and South Asians regions because of the higher metabolic syndrome prevalence [12 – 15]. Disease genetic attributes are explored in numerous allelic alterations and genetic polymorphisms research studies. Current methods for the decrease in the CVD and hypertension emphasize practice and awareness about the non-pharmacological strategies, especially exercise pattern and physical activity [16].

MATERIAL AND METHODS:

Nature of the research was cross-sectional, random which was completed in the time span of 2015 – 2017 on 528 participants. We excluded secondary hypertension cases from the record of this research. Controls and cases were respectively Normotensives and Hypertensives. We performed genotyping by tetra-primer amplification refraction mutation system by using a chain reaction of the polymerase and analysis of the data was carried out on SPSS. Informed consent was obtained from every participant. Qualified physicians were detailed for the clinical assessment of the participants. Sample was selected randomly in the guidelines of WHO sample calculator with (CI as 95%) and presumed the hypertension prevalence as (20%).

The genotype prevalence and allele frequencies of A and G were also calculated. We also analyzed genetic and risk factors size for the age factor of above fifty years, comorbid presence such as diabetes and increased BMI (> 23) which was adjusted to raise BP. For the Asian population the criteria of the BMI were used as of the Dravidian race subjects [17]. We included all the cases of who were recently diagnosed with and they were managed by anti-hypertensive intake of medicine. Any subject under the age of seven years was not made a part of the research. Research population was in the age group which was above seven years. We did not include all the cases of poor compliance, non-compliance and all who donated blood. Secondary hypertensive cases were not made a part of the research including renal, cortisone-induced, endocrinological and subjects having an incidence of diabetes. We analyzed

hypertensive subjects for stroke, diabetes development and ischemic heart disease.

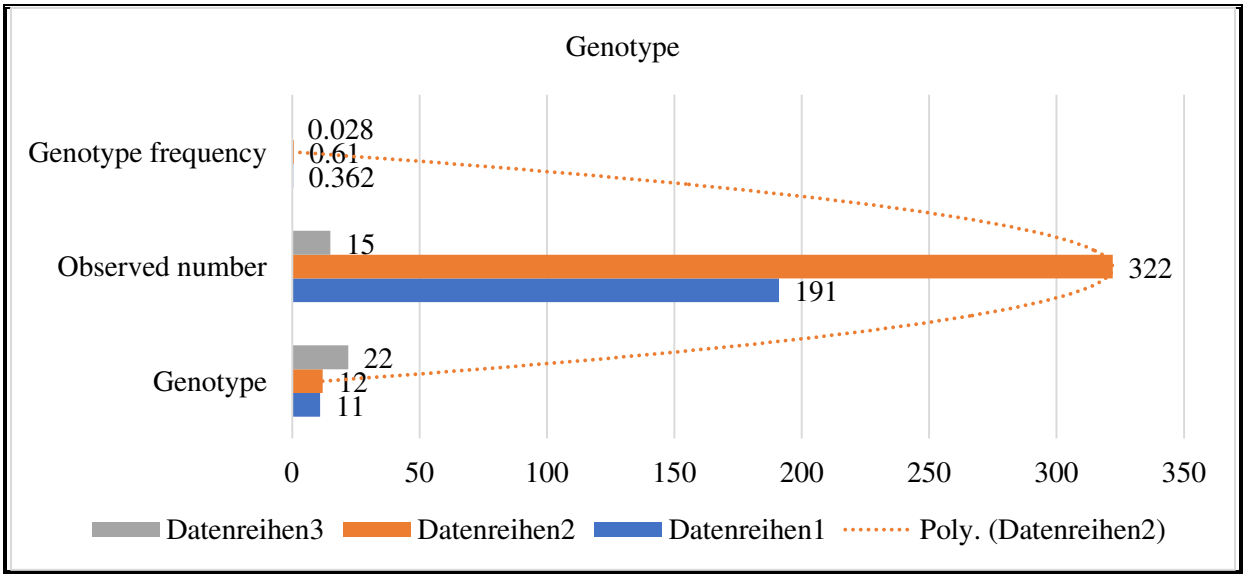
Every subject was recorded for the demographic and anthropometric. We measured three-time BP of every subject from his left arm at an interval of fifteen minutes. Hypertensive cases were those who were observed with BP as (> 140 mmHg) and diastolic BP as (> 90 mmHg) on every time as we measured BP. These hypertensive subjects were included in the cases group; whereas the controls were normotensives. We collected the samples of blood in tubes containing ethylene diamine tetra acetic acid (EDTA) subsequently stored at a temperature of (4°C).

RESULTS:

Serine Threonine Kinase – 39 (rs35929607) has an association with the critical hypertension which was measured as (3.07) (CI 95%, range 2.10 – 4.49) and in units it was described as (mmHg) / G allele (P-Value = 0.001). An elevated systolic BP (Above 140 mmHg) which reflected (0.76) (CI, 95%, 0.47 – 1.23) (P – value= 0.235) & raised diastolic Blood Pressure (> 90 mmHg) reflected as 0.93 (95% CI, 0.61 – 1.44) units/mmHg / G allele (P-value = 0.735). Risk allele G frequency was under (33.3%) in comparison to the allele – A (66.7%), (P-Value = 0.0001). Non-significant genetic factors size was observed as (0.062, P-value = 0.153), GG homozygotes (- 0.013, P-value = 0.772) and for the AG heterozygotes. Risk factors effective size was observed as (age above 50 years, diabetes and BMI above 23) had an association with the incidence of essential hypertension (0.747, P-value = 0.000). Effect was increased by (12.04 fold) in GG genotype and another three folds with the influence of the factors of risk which was required for the single allele-G in AG heterozygotes cases. Detailed outcomes analysis has been carried out in Table I, II, III and IV.

Table – I: Statistical allele frequencies, genotype frequencies and analysis of Hardy Weinberg Equilibrium

Genotype	**Observed number**	**Genotype frequency**
11	191	0.362
12	322	0.61
22	15	0.028
Total Genotyped	**528**	
Allele	**Observed number**	**Allele frequency**
1	704	0.667
2	352	0.333
Total	1056	
$\chi 2$	73.129	
p-value*	≤ 0.0001	



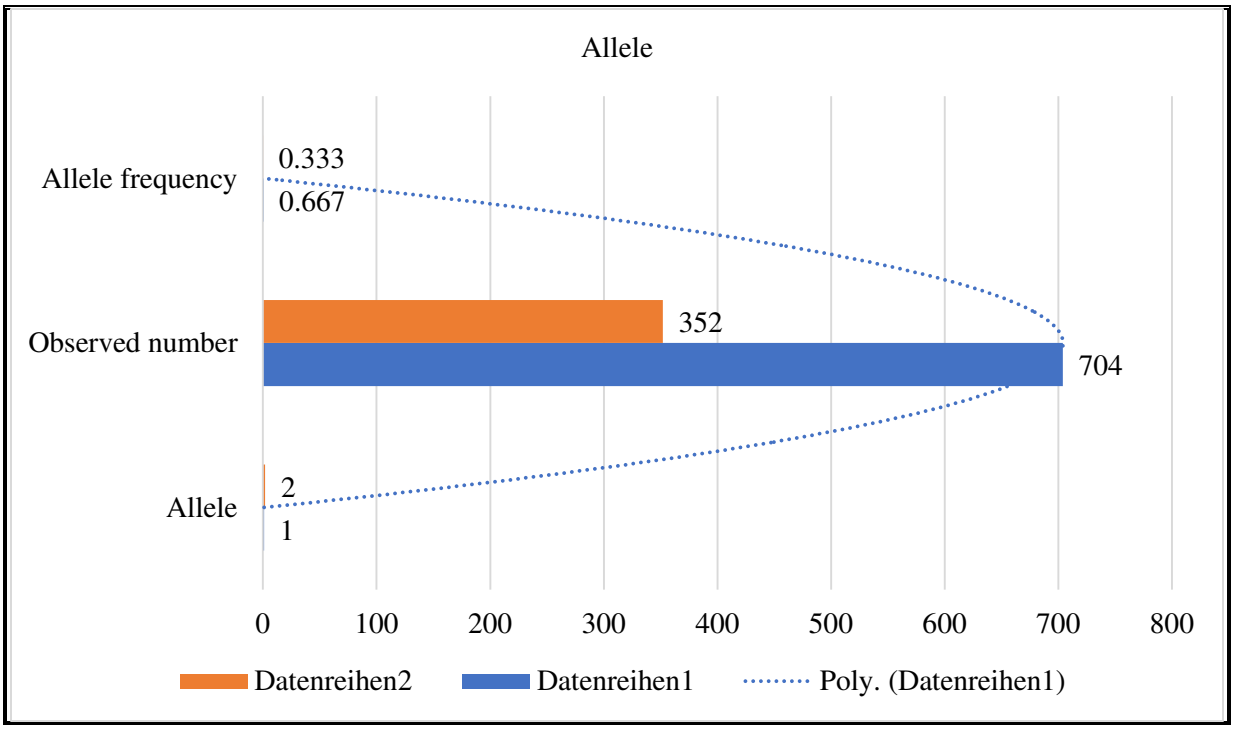


Table – II: Genotypes, allele frequencies and _2 to show significance of variables with Hardy Weinberg Equilibrium (HWE)

Basic Characteristics	AA		Genotype Frequencies		GG		Alleles Frequencies				χ^2	P-Value
	N	%	N	%	N	%	N	%	N	%		
Males	102	37	162	59	9	3	366	67	180	33	32	0.0001
Females	89	35	160	63	5	2	338	66	170	33	43.6	0.0001
Hypertensives	26	35	44	59	4	5	96	64	52	35	6.8	0.008
No hypertensives	165	36	11	2	278	61	341	37	567	62	408	0.0001
Diabetics	13	39	19	57	1	3	45	68	21	31	3.5	0.06
Non-diabetic	177	36	301	61	14	3	655	66	329	33	68.9	0.0001
Asthmatics	21	37	33	58	2	4	75	67	37	33	6.1	0.01
Non-asthmatics	168	36	13	3	285	61	349	37	583	62	412	0.0001
SBP < 140mmHg	175	36	290	60	12	3	640	67	314	32	67.6	0.0001
SBP > 140mmHg	12	28	27	64	3	7	51	60	33	39	5.07	0.02
DBP < 90mmHg	167	36	283	61	12	3	617	66	307	33	66.8	0.0001
DBP > 90mmHg	20	35	33	59	3	5	73	65	39	34	4.9	0.02

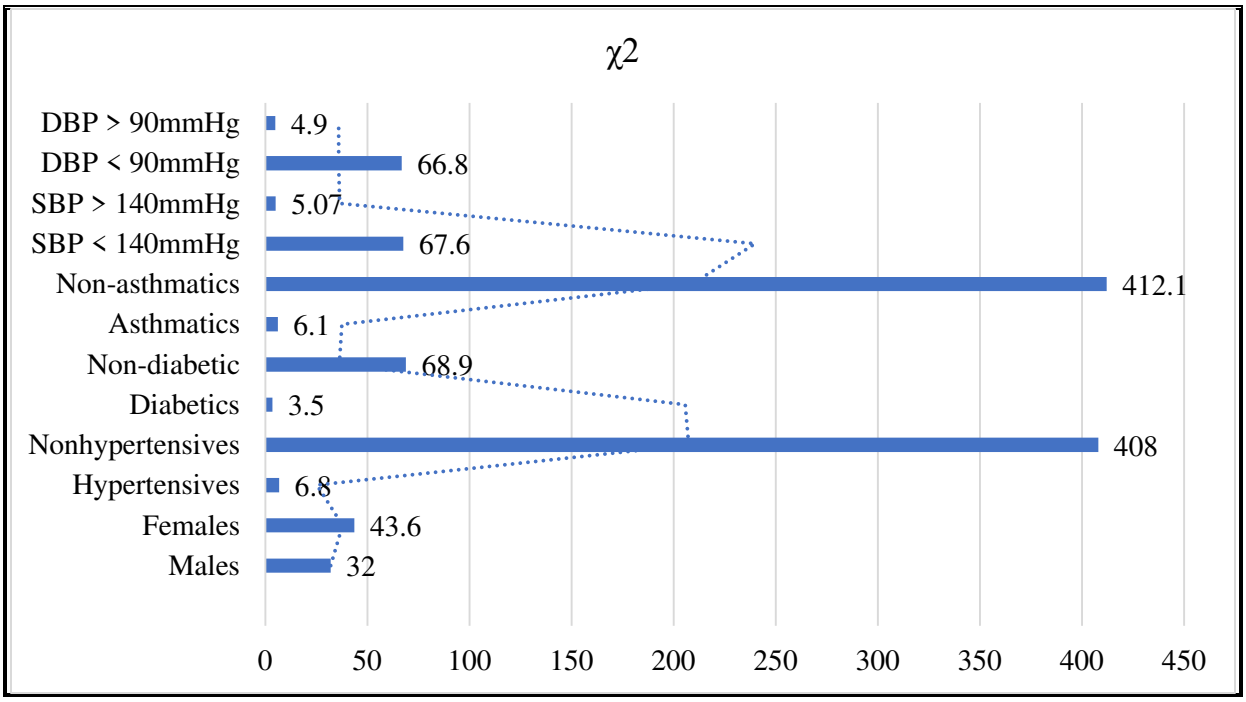
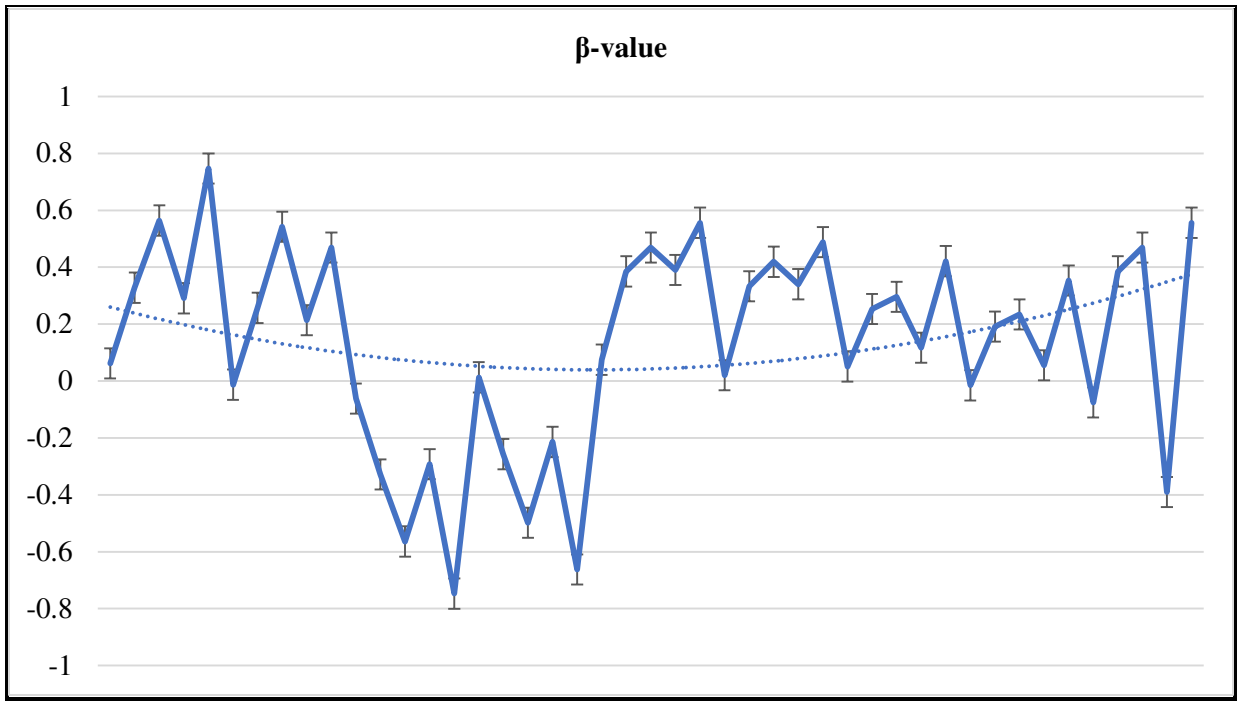


Table – III: Logistic regression determinants of main variables with frequencies of allele A and allele G

Alleles	**Comparative frequencies of cases**		**Sum**
Hypertensive		**Normotensive**	
Allele – A	96	341	437
Allele – G	52	567	619
Total	148	908	1056
Diabetics		**Non-diabetics**	**Sum**
Allele – A	45	655	700
Allele – G	21	329	350
Total	66	984	1050
Asthmatics		**Non-asthmatics**	**Sum**
Allele – A	75	349	424
Allele – G	37	583	620
Total	112	932	1044
SBP > 140mmHg		**SBP < 140mmHg**	**Sum**
Allele – A	51	640	691
Allele – G	33	314	347
Total	84	954	1038
DBP > 90mmHg		**DBP < 90mmHg**	**Sum**
Allele- A	73	617	690
Allele - G	39	307	346
Total	112	924	1036

Table – IV: Comparative analysis of STK – 39 effect size variant (rs35929607) with the risk factors effect size

Subject's Phenotype	Model	β-value	95% CI	P-Value
Hypertensives BP>140/90mmHg (Both SBP & DBP raised) GG-genotype	M1	0.062	-0.097, 0.618	0.153
	M2	0.328	0.352, 0.642	0
	M3	0.564	0.583, 10.043	0
	M4	0.291	-0.432, -0.208	0
	M5	0.747	0.104, 0.216	0
Hypertensives BP>140/90mmHg (Both SBP & DBP raised) AG-genotype	M1	-0.013	-070, 0.052	0.772
	M2	0.257	0.360, 0.650	0
	M3	0.542	0.579, 10.040	0
	M4	0.214	-0.427, -0.203	0
	M5	0.469	0.102, 0.213	0
Normotensives BP<140/90mmHg (Both SBP & DBP normal) GG-genotype	M1	-0.062	-0.309, 0.048	0.153
	M2	-0.328	-0.321, -0.176	0
	M3	-0.564	-0.521, -0.291	0
	M4	-0.292	0.104, 0.216	0
	M5	-0.747	-0.108, -0.052	0
Normotensives BP<140/90mmHg (Both SBP & DBP normal) AG-genotype	M1	0.013	-0.026, 0.035	0.772
	M2	-0.257	-0.325, -0.180	0
	M3	-0.498	-0.520, -0.290	0
	M4	-0.214	0.102, 0.213	0
	M5	-0.662	-0.107, -0.051	0
Raised SBP(>140mmHg) GG-genotype	M1	0.075	-0.035, 0.526	0.086
	M2	0.385	0.340, 0.565	0
	M3	0.469	0.041, 0.411	0.017
	M4	0.39	-0.182, 0.001	0.052
	M5	0.556	0.000, 0.091	0.052
Raised SBP(>140mmHg) AG-genotype	M1	0.02	-0.037, 0.059	0.657
	M2	0.333	0.344, 0.569	0
	M3	0.419	0.040, 0.410	0.017
	M4	0.34	-0.177, 0.005	0.065
	M5	0.488	-0.003, 0.089	0.065
Raised DBP(>90mmHg) GG-genotype	M1	0.051	-0.131, 0.509	0.246
	M2	0.253	0.204, 0.469	0
	M3	0.296	-0.087, 0.351	0.238
	M4	0.117	-0.301, -0.082	0.001
	M5	0.421	0.041, 0.150	0.001
Raised DBP(>90mmHg) AG-genotype	M1	-0.015	-0.064, 0.046	0.737
	M2	0.191	0.210, 0.475	0
	M3	0.234	-0.090, 0.348	0.249
	M4	0.055	-0.298, -0.079	0.001
	M5	0.353	0.039, 0.149	0.001
Normal SBP(<140mmHg) GG-genotype	M1	-0.075	-0.263, 0.018	0.086
	M2	0.385	-0.282, -0.170	0
	M3	0.469	-0.205, -0.020	0.017
	M4	-0.39	0.000, 0.091	0.052
	M5	0.556	-0.045, 0.000	0.052



DISCUSSION:

Essential hypertension is among the well-known environmental and genetic disorder which has a role in the etio-patho-genesis [20]. All over the globe its incidence is varying. The population of India and Pakistan reflect a lower prevalence of hypertension; whereas, in Poland is it reported very high in men and women respectively 68.9% & 72.5% [21]. In the African-American countries the mortality and morbidity in increased proportion is caused by the coronary artery disease [22 – 24]. South Asian countries reflect higher mortality rates than the Caucasians which is not dependent on the religion, gender, social class, residence and diet habits [24]. We found its prevalence in Pakistan as (22.7%). In the current population of research, the incidence was observed as (14.3%). There was a coincidental incidence of relation between systolic and diastolic BP and (STK – 39 gene) SNP rs35929607 with a significant P-value as (< 0.05) [5]. There was also an insignificant association of the essential hypertension and polymorphism (P-value as 0.153). We observed (STK – 39 SNP) prevalence and we also observed reference frequencies including rare alleles in concordance to the HWE. Locus of the STK39 is located in the area of genome which doubles the BP, diabetes and obesity. Hypertensive tendency can be explained through this locus [25]. It has been proved that exercise and physical activity help in the reduction of hypertension about (75%) [24]. A predominant factor is also attributed to environmental and genetic factors.

Blood pressure is significantly affected by the incidence of environmental risk factor size specially in case of BMI (< 23), increased age (> 50 years) and diabetes. Logistic and Linear regression analyses also indicate BMI as the contributing factor to control BP. With the treatment of increased dyslipidemia, BMI and hypertension; thus, risks of CVD and EHTN are also increased.

CONCLUSIONS:

Risk of the essential hypertension as observed by polymorphism as observed in our research was not same as it was reported previously by a European author. It was suggested that variant G allele has a weak association when the environmental risk factors are absent. There was a difference in the study of the hypertension risk conferred by (STK – 39 rs35929607) polymorphism (A/G) in our research and as stated in the European research.

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