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ASSOCIATIONS OF SINGLE NUCLEOTIDE POLYMORPHISMS (RS7539542, RS7514221, RS3737884 AND RS1342387) OF RECEPTORS OF ADIPONECTIN WITH HYPERLIPIDEMIA IN PATIENTS WITH TYPE 2 DIABETES

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Keywords : *SNP: Single nucleotide polymorphism, PCR-RFLP: Polymerase chain reaction restriction fragment length polymorphism, ADIPOR1 : Adiponectin receptor one SLP: Serum lipid profile, BGL: Blood glucose level, IR: Insulin resistance*

Abstract–Type 2 diabetes is disorder that is characterized by uncontrolled elevation the level of glucose that induce complications that may threat the life and the quality of life in those that suffer from the abnormal action of insult and so may induce many healthy problems that could lead eventually to death this disease induced by many genetic and environmental factors. Some of these genes found in different chromosomes weather coding, non-coding and even un translated region. One of these gene is diponectin receptor one gene. Genetic variant of this receptor may induce a healthy problems and may lead to any diseases like cardiovascular disease, cancer, diabetes and other. To predict whether or not that diponectin receptor1 genetic variants have an effect on biochemical parameters in patient with diabetes. In case control study that conducted in Kufa University, Department of clinical chemistry. eight hundred individuals (400 control volunteer in addition to another 400 DM patients were enrolled in the study. 5 milliliter of blood was taken and divided in to two milliliter that kept in serum tube for biochemical measurements in addition to three milliliter put in EDTA tube for DNA extraction. DNA extraction was done to measure gene variants (SNP) of adiponectin receptor 1 (rs7539542,rs7514221, rs1342387 and rs3737884) followed by amplification by PCR-RFLP then electrophoresis by 2 % agarose gel phenotypic measurements was done for SLP, BGL, IR data was analyzed by SPSS version 20. Data indicate that the four SNPs have insignificant effect on BMI but shows different correlations with SLP, insulin resistance and blood glucose level.

INTRODUCTION

Diabetes mellitus is a metabolic disorder that induce an effect on humankind due to its micro and macro vascular complication that happened under the effect of hyperglycemia with an increment in the amount of people that suffer from DM in the last decade there is an important issue to speculate and to understand why such a disease occurrence and how to stop its complication and reduce its spread in population and as it considered as a risk disease in Iraq society at which more than 10 % of Iraqi population suffer from DM so its important thing to make more focus on this disease, at least genetically and phenotypically (Parks and Hellerstein, 2006; Preeti and Malani, 2012; Shoback *et al.,* 2011; Nj *et al.,* 2011).

Many genes is studies in Iraq that are of interest on DM which include resistin, adiponectin, FTO, MTHFR and many other genese, but till now no study has made an attention on adiponectin receptor effect in Iraqi population the gene encode for adiponectin receptor 1 located on chromosome 1 at the long arm telomere (q), it has a physiological effect on insulin resistance and regulation carbohydrate and lipid metabolism. Adiponectin bind to globular adiponectin receptor and so regulate lipid m carbohydrate and insulin function . Any defect in this function may induce obesity and hyperlipidemia and hyperglycemia and finally DM

(Dorajoo *et al.,* 2015); (Ayub *et al.,* 2014); (Manuscript, 2014); (Weigert *et al.,* 2008) (SCALIA BJGAR, 2004); (Yamauchi *et al.,* 2003)(Robert *et al.,* 2011)(Yamauchi *et al.,* 2014) (www.NCBI.com) adds a supporting to previous study that are conducted in many societies in different countries like America, Russia, France and other this study conducted in a hope to discover the genetic effect of this receptor at which this genetic variant may be a causative factor and its complication in addition to the effect that may occurs in human weight and health and metabolic regulations factor for development of DM (Bermúdez *et al.,* 2008); (Rasmussen-torvik *et al.,* 2009); (Jin *et al.,* 2014); (Richardson *et al.,* 2006); (Damcott *et al.,* 2005); (Halvatsiotis *et al.,* 2010).

METHODS

Selection of forward and reverse primer in addition to the annealing temperature was measured and approved for accurate benefit results that could be collected. After receiving the forward and reverse primers, the DNA extracted according to the kit procedure by mixing 12.5 µL of master mix with 1.5 µl of both forward and reverse primers and 6 µL of extracted, pure DNA sample and finally complete the volume to 25 µL using deionized water the thermo cycling occur by a special apparatus (thermo cycler) digestion was done by using the appropriate enzymes and incubation fallowed by electrophoresis in agarose gel using the safe stain and finally capture of the picture was observed by UV transilluminator The horizontal electrophoresis was occur by two percent agarose gel at (75volt and and120 min) and directly visualized with acidic diamond dye under UV light**.** using the gel imaging system (UV transilluminator) (UVP (UK)) (Figure 1, 2, 3 and 4) (Table 1 and 2)

Variables was measured in means ± standard deviation using SPSS software program version 20. Clinical characteristic were measured using Student's t-test or analysis of variance test, Pearson's x^2 analysis for categorical variables. Measurements of for (HWE) were performed. MAF was calculated using Hardy-Weinberg Equilibrium Calculator for 2 Alleles dominant and recessive models was occurs using Web-Assotest after collection the wild, heterozygous and homozygous of each SNP in both groups. Odds ratio (OR) and confidence intervals (CI) was calculated by online program from www.medcalc.net and at the beginning the data of

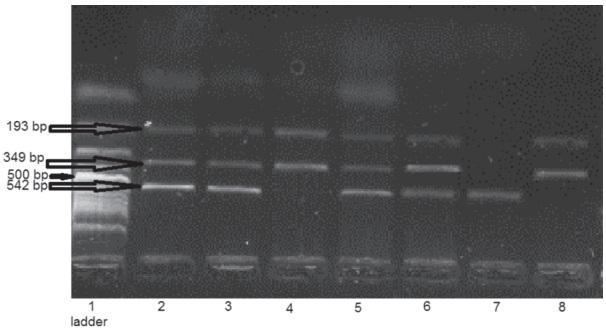

Fig. 1. Electrophoretic product of adiponectin receptor 1 polymorphism rs7539542 after digestion with *BsmaI* and electrophoresis with 1.5 % agarose at 75 volt for 120 minute

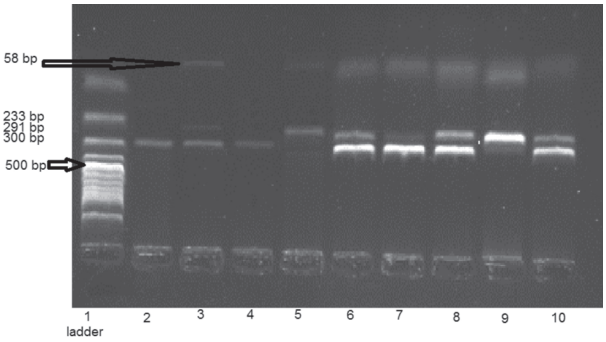

Fig. 2. Electrophoretic product of adiponectin receptor 1 polymorphism rs7514221 after digestion with *HaeII* and electrophoresis with 1.5 % agarose at 75 volt for 120 minute

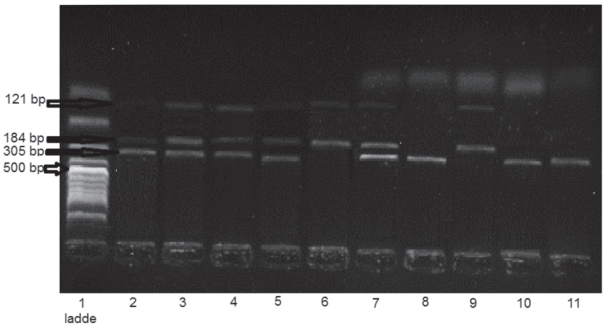

Fig. 3. Electrophoretic product of adiponectin receptor 1 polymorphism rs3737884 after digestion with *PleI* and electrophoresis with 1.5 % agarose at 75 volt for 120 minute

estimation sample size was based on online program called online sample size estimator (POSSE),

RESULTS

Tn Table 3 the biochemical characteristics of both

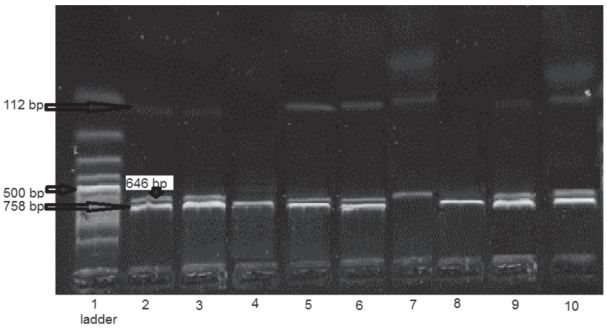

Fig. 4. Electrophoretic product of adiponectin receptor 1 polymorphism rs1342387 after digestion with *BccI* and electrophoresis with 1.5% agarose at 75 volt for 120 minute

groups was enrolled and shows a significant difference (P value ≤ 0.05) between diabetic and control individual in case of age, lipid profiles, BGL, IR and BMI. This Table demonstrates that diabetic patients suffer from abnormal carbohydrate and lipid metabolism (hyperglycemia and hypercholesterolemia etc.) and this highly elevated results encourage the proceeding of discovering the prognostic factor that leads to such abnormal pathological results that occurs in such patients that may be the prognostic factor for exposure to DM.

The minor allele frequency (MAF) was calculated depending on the online programs that are mentioned previously and show P value > 0.05 in control people also the complete criteria if each SNP was mentioned in this Table including the annealing temperature, restriction enzyme, amplicon length, major (ancestral) allele and the minor (risk) allele (Table 1 and 4).

SNP association analysis

These SNPs were analyzed using dominant, co dominant and recessive models with relation to occurrence of diabetes which revealed that the risk effect of rs3737884 and rs7514221 is increased by six and two folds respectively while there is no effect of rs7539542 and rs1342387 on the prognosis of DM on the other =hand all of the four SNPs have insignificant effect on BMI, but vary in their effect on the other biochemical measurements , the reason is unknown but may be due to the genetic diversity between Iraqi and other populations (**5-17)**

These findings show a significant correlation between adiponectin receptor 1 (rs3737884) with exposure to DM at which there is increment in the exposure to this disease in about four times in the presence of this SNP (OR =4.89, (P-values 0.000))

Table 1. Criteria of each single nucleotide polymorphism that enrolled

SNP	Allele	Enzyme	Annealing temp. (^{0}C)	Amplicon length of PCR (bp)	Fragment (bp) after cutting	Cutting site (5'- 3')	Primer sequences
Rs 7539542	G.A	BsmaI	65	542	349/193	GTCTC(N)	F 5- GCACCCAGCCCTGAGAATCT -3 R 5- CCGGCTAATCATGGAAGTGTGT -3
Rs 7514221	T.C	HaeII	58	291	233/58	GCGC!	F 5- ACAACCTCAGGAACCGAAGT -3R 5- GGAGAATGGGAAACTGACAA -3
Rs1342387	G.A	BccI	58	758	646/112	CCATC$(N)_4$	F 5- CCCGCTTCTAAGTCTCCAT -3R 5- TGAAGTACATATTTGGTCTGA -3
Rs3737884	C.T	PleI	56	305	121/184	GAGTC$(N)_4$	F-5- AGTAAGGGAAAGGGATAGAGT-3R- 5-TAATAGAGCCAGGGGACAAA-3

and two folds in case rs7514221, the reason is unknown it may be due to ethnicity or genetic specify of this SNP on the Iraqi population or may be by the effect on insulin resistance as mentioned previously on the other hand the significant difference in the levels of theses parameters in the presence of this genetic variant when compared in the absence of this SNP. Rs3737884 has an effect also on lipid profile that indicate increase level of cholesterol, TG (except LDL cholesterol) and decrease level of HDL when compared with control group both of these two polymorphisms shows non-significant correlation with BMI the reason is also unknown but may be due to diversity of this population when compared with other populations. Rs1342387 has no effect on occurrence of DM and not significant correlation after adjustment of dominant and recessive models in relation to age and sex this SNP has no risk factor nor protective for development of DM as such this resulted that occurrence of DM is may attributed to other factors that is not related to the gene variant of this SNP.

Haplotype analysis : Data concerned with the frequency of more than one SNP in the same individual in relation to biochemical criteria showed that there is insignificant correlation between each haplotype and the biochemical measurements , it revealed that the chance of presence of more than one genetic variants at the same person does not increase the hazard of disease nor it effect on the carbohydrate and lipid metabolism so it had no effect on factor weather genetic or environmental that may produce health problems and again the cause may be related to ethnic diversity between populations (Table 5-8)

The result of these two SNPs are in consistence with other study produced in Mexican American(16), northern European, (13) African American(19) Francis Caucasian (20), UK, European, African Japanese (21) (Vaxillaire *et al.*,

Table 2. Mixture preparation of PCR products of adiponectin receptor 1 SNPs

SNP	Restriction enzyme (µg)	DNA (µL)	10 X NE Buffer (µL)	Total Rx volume (µL)	Incubation temp. and time
Rs7539542	1	1	5	50	55 °C for 5-15 min
Rs7514221	0.5	1	2	20	37 °C for 60 min
Rs3737884	2	1	5	50	37 °C for 60 min
Rs1342387	1	1	5	50	37 °C for 60 min

Table 3. General biochemical criteria of selected obese individuals

Parameters	Control	T_2DM	P value
No (M/F)	400 (210/190)	400 (215/185)	**0.7918**
Age (y)	55.93±4.608	59.5±12.96	0.000
BMI ($kg/m^{2)}$)	33.7±3.34	33.86±4.17	0.000
FBS (mg/dl)	100.69±15.39	238.69±20.80	0.000
Cholesterol (mg/dl)	139.41±24.37	265.41±25.32	0.000
Triglycerides (mg/dl)	123.42±14.53	250.87±26.889	0.000
VLDL (mg/dl)	25.08±5.51	52.63±7.51	0.000
LDL (mg/dl)	86.10±28.05	152.66±24.88	0.000
HDL (mg/dl)	57.54±6.236	50.37±7.24	0.000
Fasting plasma insulin (µU/mL)	12.46±2.95	29.66±2.71	0.000
HOMA index	11.503±2.51	14.96±1.59	0.000

Table 4. Single nucleotide polymorphism criteria ("www.genenames.org/HUGO," 2016)("www.ncbi.nlm.nih.gov," 2016)

SNP	Rs7539542	Rs7514221	Rs1342387	Rs3737884
minor allele	G	T	G	G
Ancestral allele	C	C	A	A
location	1:202940846	1:202957385	1:202945228	1:202944076
Functional Consequence	UTR variant 3 prime	intron variant	intron variant	intron variant
MAF	26.6	19.7	37.3	14.2
HWE P value	0.06	0.089	0.191	0.113

Table 5. Haplotype sequence of adiponectin receptor 1 polymorphisms (note: 0 numbers in each haplotype represent the presence of gene before occurrence of its variation, i.e., polymorphism while 1 numbers represent the occurrence of its polymorphisms

Haplotype code	Rs7539542	Rs7514221	Rs1342387	Rs3737884	Haplotype sequence
1(Ref)	0	0	0	0	0000
2	0	0	1	0	0010
3	0	1	1	0	0110
4	0	1	1	1	0111
5	1	0	1	0	1010
6	1	1	1	0	1110
7	1	1	1	1	1111

Table 6. Haplotype distribution in obese type 2 diabetes and healthy

Haplotype Code	Frequency (DM/Control	Number (DM/Control)	P value
1	0.58/0.63	233/250	0.219
2	0.11/0.11	42/43	0.842
3	0.02/0.00	8/0	0.004
4	0.0125/0.00	5/0	0.027
5	0.00/0.0925	0/37	0.000
6	0.00/0.0325	0/13	0.000
7	0.28/0.14	112/57	0.000

Table 7. Correlation of haplotype of adiponectin receptor 1 polymorphisms with phenotypic changes in obese type 2 diabetic individuals

Haplotype code No	1 233	2 42	3 (8)	4 (5)	7 (112)	P value
Age	60.53±8.36	58.63±8.3	59.35± 9.63	61 ±9.14	58.67±11.3	0.427
BMI	33.81±4.31	32.96±3.41	35.997±4.2	32.82±3.16	34.17±4.12	0.248
HDL	41.25±7.29	41.96±7.48	42.64±5.88	38.24±8.22	41.45±7.15	0.821
VLDL	51.71±7.89	53.84±6.36	52.64±10.3	46.98 ±7.74	53.01±6.77	0.152
TG	255.34±24.7	266.2±29.68	252.88±38.6	246.2±24.96	259.58±28.6	0.381
TC	255.27±24.3	259.3±25.30	250.25±28.8	248.4±10.62	257.16±24.3	0.769
BGL	237.3±20.86	245.3±18.2	232.25±26.5	231.6±22.35	240.39±20.8	0.1177
LDL	152.95±26.2	155.34±29.7	147.04±29.1	150.92±20.1	153.79±25.3	0.857

Table 8. Effect of haplotype of adiponectin receptor 1 polymorphisms biochemical changes in obese control volunteers

Parameter Haplotype No	‘ 1 250	 2 43	 5 (37)	 6 (13)	 7 (57)	P value
Age	56.95± 8.65	62.5± 7.2	54.51±8.65	55.23±7.61	54.62±9.4	0.0001
BMI	32.94±3.41	32.7±3.98	31.8±3.79	32.50±2.55	32.79±2.2	0.4277
HDL	67.49±7.35	67.6±7.1	67.5±7.94	68.74±5.6	67.5±6.9	0.984
VLDL	26.37±7.8	27.4±7.3	26.16±8.09	28.08±4.8	28.36±6.3	0.3803
TG	139.5±23.17	138.6±31.2	137.95±22.2	143.4±26.4	139.7±28.4	0.97
TC	157.6±24.07	150.5±26.2	161.27±25.1	162.1±25.41	158.1±22.9	0.293
BGL	90.64±15.81	91.97±16.1	94.14±13.84	96.92±11.6	94.72±14.3	0.2178
LDL	86.36±26.19	79.29±26.2	90.31±26.55	88.78±27.26	86.8±24.68	0.392

2006)(23), Japanese population (24), black and white women (25), (26) (27) Chinese population (15)(28) Northeast Han Chinese Population (29).

CONCLUSION

Rs1342387 and Rs7539542 have no effect on occurrence of DM in Iraqi population while rs3737884 is a risk factor that effect on incidence of diabetes four times. Further works should be done on the effect of those two polymorphisms on different disease especially breast cell carcinoma, colorectal carcinoma, cardiovascular diseases

Key points

1. Adiponectin receptor one gene polymorphism play an important prognostic effect on development of diabetes and so a full detailed study was done
2. Further researches on the effect of each genetic variant was done in relation to anthropometric measurements and so its effect on theses parameters was observed
3. Dominnant, Codominant and recessive models of each type of SNPs was calculated in addition to measurement of adds ratio to speculate the adjusted and unadjusted effect of each SNP in relation to the age and sex.

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REFERENCES

Ayub, Q., Moutsianas, L., Chen, Y., Panoutsopoulou, K., Colonna, V. and Pagani, L. 2014. Revisiting the Thrifty Gene Hypothesis via 65 Loci Associated with Susceptibility to Type 2 Diabetes. *Am J Hum Genet* [Internet]. 94(2): 176–185. Available from: http://dx.doi.org/10.1016/j.ajhg.2013.12.010

Bermúdez, V.J., Rojas, E., Toledo, A., Rodríguez-Molina, D., Vega, K. and Suárez, L. 2008. Single-nucleotide polymorphisms in adiponectin, AdipoR1, and AdipoR2 genes: insulin resistance and type 2 diabetes mellitus candidate genes. *Am J Ther* [Internet]. 2008; 20(4) : 414–421. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23656997

Cohen, S.S., A, Marilie D. Gammon PD (Advisor). Select Environmental and Genetic Determinants of Adiponectin and Obesity in Black and White Women. 2010.

Collins, S.C., Luan, J., Thompson, A.J., Daly, A., Semple, R.K. and O'Rahilly, S. 2007. Adiponectin receptor genes: Mutation screening in syndromes of insulin resistance and association studies for type 2 diabetes and metabolic traits in UK populations. *Diabetologia.* 50(3) : 555-562.

Damcott, C.M., Ott, S.H., Pollin, T.I., Reinhart, L.J., Wang, J. and O'Connell, J.R. 2005. Genetic variation in adiponectin receptor 1 and adiponectin receptor 2 is associated with type 2 diabetes in the Old Order *Amish 4. Diabetes.* 54(0012–1797 (Print)): 2245–2250.

Dorajoo, R., Liu, J. and Boehm, B.O. 2015. Genetics of Type 2 Diabetes and Clinical Utility. *Genes (Basel).* 6 : 372–384.

Halvatsiotis, I., Tsiotra, P.C., Ikonomidis, I., Kollias, A., Mitrou, P. and Maratou, E. 2010. Genetic variation in the adiponectin receptor 2 (ADIPOR2) gene is associated with coronary artery disease and increased ADIPOR2 expression in peripheral monocytes. *Cardiovasc Diabetol*. [Internet]. 2010;9:10. Available from: http://www.pubmedcentral.nih.gov/articlerender. fcgi?artid=2846898&tool=pmcentrez&rendertype=abstract

Hara, K., Horikoshi, M., Kitazato, H., Yamauchi, T., Ito, C. and Noda, M. 2005. Absence of an association between the polymorphisms in the genes encoding adiponectin receptors and type 2 diabetes. *Diabetologia.* 48(7) : 1307–1314.

Jin, Z., Pu, L., Sun, L., Chen, W., Nan, N. and Li, H. 2014. Identification of susceptibility variants in ADIPOR1 gene associated with type 2 diabetes, coronary artery disease and the comorbidity of type 2 diabetes and coronary artery disease. *PLoS One.* 9(6).

Kaklamani, V.G., Sadim, M., Hsi, A., Offit, K., Oddoux, C. and Ostrer, H. 2008. Variants of the adiponectin and adiponectin receptor 1 genes and breast cancer risk. *Cancer Res.* 68(9) : 3178–3184.

Manuscript A. 2014. Diabetes Treatment — Bridging the Divide Dr. *N Engl J Med.* 356(15) : 1499–1501.

Nj, M., Sl, W., Lk, S., Jh, F. and Keen, H. 2001. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia.* 44 : 14–21.

Norbert Stefan, Peter Weyrich, Hans –Ulrich, Markku Laakso 2007. Effect of genotype on success life style intervention in subjects at risk of type 2 diabetes. *J. J Mol Med.* 85 : 107–117.

Parks, E.J. and Hellerstein, M.K. 2006. Thematic review series: patient-oriented research. Recent advances in liver triacylglycerol and fatty acid metabolism using stable isotope labeling techniques. *J Lipid Res*

[Internet]. 47(8) : 1651–1660. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16741290

Preeti, N. and Malani, M.D. 2012. MSJ M. Harrison' s Principles of Internal Medicine. *JAMA.* 308(17) : 1813–1814.

Rasmussen-torvik, L.J., Pankow, J.S., Jr, D.R.J., Steinberger, J., Moran, A. and Sinaiko, A.R. 2009. The Association of SNPs in ADIPOQ, ADIPOR1, and ADIPOR2 with Insulin Sensitivity in a Cohort of Adolescents and their Parents. *Hum Genet.* 125(1) : 21–28.

Richardson, D.K., Schneider, J., Fourcaudot, M.J., Rodriguez, L.M., Arya, R. and Dyer, T.D. 2006. Association between variants in the genes for adiponectin and its receptors with insulin resistance syndrome (IRS)-related phenotypes in Mexican Americans. *Diabetologia.* 49(10) : 2317–2328.

Robert, J., Ferry, J., Hale, P.M., Cushman, T.T., Kimball, E.S. and Nair, A. 2011. *Management of Pediatric Obesity and Diabetes.* Springer New York Dordr Heidelb. 1-24.

SCALIA BJGAR, 2004. Dorrance. Adiponectin/: A Novel Adipokine Linking Adipocytes and Vascular Function. 89(6) : 2563–2568.

Shoback, David G. and Gardner, D. 2011. *Greenspan's Basic & Clinical Endocrinology* (9th ed.). 2011. chapter 17.

Siitonen, N., Pulkkinen, L., Mager, U., Hämäläinen, H., Ilanne-Parikka, P. and Keinänen-Kiukaanniemi, S. 2006. Association of sequence variations in the gene encoding adiponectin receptor 1 (ADIPOR1) with body size and insulin levels. The Finnish Diabetes Prevention Study. *Diabetologia.* 49(8) : 1795–1805.

Vaxillaire, M., Lahmidi, S., Vatin, V., Boutin, P., Hercberg, S. and Charpentier, G. 2006. Genetic Analysis of ADIPOR1 and ADIPOR2 Candidate Polymorphisms for Type 2 Diabetes in the Caucasian Population. *Diabetes.* 55 : 856-861.

Vaxillaire, M., Lahmidi, S., Vatin, V., Boutin, P., Hercberg, S. and Charpentier, G. 2006. Genetic Analysis of ADIPOR1 and ADIPOR2 Candidate Polymorphisms for Type 2 Diabetes in the Caucasian Population Martine. *DIABETES.* 55: 856–861.

Wang, F., Suo, S., Sun, L., Yang, J., Yang, F. and Zhao, C. 2016. Analysis of the Relationship Between ADIPOR1 Variants and the Susceptibility of Chronic Metabolic Diseases in a Northeast Han Chinese Population. *Genet Test Mol Biomarkers.* 20(2) : 81–85.

Wang, H., Zhang, H., Jia, Y., Zhang, Z. and Craig, R. 2004. Adiponectin receptor 1 gene (ADIPOR1) as a candidate for type 2 diabetes and insulin resistance. *Diabetes* [Internet]. 53(August). Available from: http://diabetes.diabetesjournals.org/content/53/8/2132.short

Weigert, J., Neumeier, M., Wanninger, J., Wurm, S., Kopp, A. and Schober, F. 2008. Reduced response to adiponectin and lower abundance of adiponectin receptor proteins in type 2 diabetic monocytes. *FEBS Lett.* 582(12) : 1777–1782.

Yamauchi, T., Iwabu, M. and Okada, M. 2014. Adiponectin receptors: a review of their structure, function and how they work. *Best Pr Res Clin Endocrinol Metab.* 28: 15–23.

Yamauchi, T., Kamon, J., Ito, Y., Tsuchida, A., Yokomizo, T. and Kita, S. 2003. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature.* 423(6941) : 762–769.

Yu, L.X., Zhou, N.N., Liu, L.Y., Wang, F., Ma, Z.B. and Li, J. 2014. Adiponectin receptor 1 (ADIPOR1) rs1342387 polymorphism and risk of cancer: A meta-analysis. *Asian Pacific J Cancer Prev.* 15(18) : 7515–7520.