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Data Analysis of Single Nucleotide Polymorphism in Human *AGT* Gene Using Computational Approach

Mohammed Youssif Mohammed, Afra Mohamed Al Bkrye, Hind Abdelaziz Elnasri, Mona Abdelrahman Mohamed Khaier*

Department of Molecular Biology and Bioinformatics, College of Veterinary Medicine, University of Bahri, Khartoum, Sudan

Email address:
munakhaier@gmail.com (M. A. M. Khaier)
*Corresponding author

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Abstract: *Background*: The *AGT* gene is gene responsible for regulation of protein called angiotensinogen which regulates blood pressure and balances fluids in the body. Hypertension happens due to many causes one of this is the defect in *AGT* gene. Hypertension usually has no symptoms. However, it is a major risk factor for heart diseases, stroke, kidney failure, and eye problems. *Objectives*: in this study we use software to analyze the gene using different software and represented statistically and to detect the SNPs that can cause the disease. *Material and Method*: In this analysis using many software tools that can analyze the nsSNPs retrieved from NCBI website. These software include SIFT, I-mutant, Polyphen-2, PHD SNP and SNP& Go, Projecthop and GeneMANIA. *Results*: The study showed that from 172 nsSNPs only 46 nsSNPs were deleterious while 126 were tolerated using SIFT. Two were benign, 11 were possibly damaging and 33 were probably damaging by Polyphen-2. Using Provean, 19 nsSNPs were neutral and 27 were deleterious. For PHD-SNP software 20 nsSNPs were disease related and 18 were neutral. Also SNPs were checked using SNP & Go software that showed 32 neutral nsSNPs and 14 nsSNPs were disease associated variants. Using I-Mutant software 13 nsSNPs increase the stability of the protein and 33 decrease the protein stability. *Conclusions*: In conclusion, extensive functional and structural analyses are carried out to predict potentially damaging and deleterious nsSNPs of *AGT* gene using bioinformatics and computational methods. In the study, 14 high confidence damaging nsSNPs are identified from 172 nsSNPs. Although bioinformatics tools have their limitations, the results from the present study may be convenient in future for further population based research activities and towards development of accuracy medicines.

Keywords: *AGT* Gene, Hypertension, I-mutant, SIFT, SNP & Go and PHD, Polyphen-2, Provean and Project Hope, SNP

1. Introduction

AGT is a gene use to control type of protein called angiotensinogen, which represent a part of angiotensin system, that function to regulate blood pressure and fluid in the body [1]. This regulation happens by converting angiotensinogen into angiotensin I [1]. And angiotensin I is converted into angiotensinogen II, that cause blood vessels to narrow leading to increase in blood pressure [2]. Also angiotensinogen II induce production of aldosterone hormone [2], which plays a role in salt absorption by kidney [1], leading to increase body fluids hence increase in blood pressure [3]. Normal blood pressure is important during fetal life which delivers oxygen to body tissue, also need it for kidney development especially the proximal tubules and growth factors involving in kidney structure. [4].

Many health conditions associated with the disease were caused by mutation in *AGT* gene, among these is hypertension, a specific mutation in *AGT* gene causes the disease [5]. However, hypertension is a major risk factor for heart disease, stroke, kidney failure, and eye problems. When blood pressure is elevated, the heart and arteries have to work harder than normal to pump blood through the body [6]. The extra work thickens the muscles of the heart and arteries and hardens or damages artery walls [7]. As a result, the flow of blood and oxygen to the heart and other organs is reduced.

2. Material and Methods

Data retrieval: this was done using the dbSNP (http://www.ncbi.nlm.nih.gov/SNP/). Information regarding SNPs of *AGT* gene was obtained during the year 2019. Interaction of this gene with other genes was investigated using GeneMANIA. Functional effect of the nsSNPs on the protein was investigated using SIFT, Polyphen-2, and Provean. The stability of the protein as the result of the mutation was studied using I- Mutant lastly the effect of the SNPs on the structure was predicted using Project hope.

2.1. GeneMANIA

(http://www.genemania.org) [8]. It is a web interface that finds other genes related to a set of input genes, using a very large set of functional association data. Gene name was entered into the software and the result show that an association data include protein and genetic interactions, pathways, co-expression, co-localization and protein domain similarity.

2.2. SIFT (Sorting Intolerant from Tolerant) http://blocks.fhcrc.org/sift/SIFT.html [9]

It is an online tool that predicts if an amino acid substitution affects protein function or not by using sequence homology. The dbSNP that were retrieved from NCBI were entered into the software and the result appears as deleterious or not according to whether amino acid substitution affects protein function based on sequence homology and the physical properties of amino acids.

2.3. Polyphen-2 (Polymorphism Phenotyping v2)

http://genetics.bwh.harvard.edu/pph2/. It is used to predict the possible impact of an amino acid substitution on both structure and function of protein by analysis of multiple sequence alignment and protein 3D structure [1]. The software estimates the position specific independent count score (PSIC) for every variant and then determines the difference between them, the higher the PSI, the higher the functional impact of the amino acid on the protein function may be. Prediction outcomes could be classified as probably damaging, possibly damaging or benign according to the score ranging from (0-1).

2.4. Provean (Protein Variation Effect Analyzer)

(http://provean.jcvi.org/index.php). It is a software tool which predicts whether an amino acid substitution has an impact on the biological function of a protein. SNPs were entered using protein sequence. The Prediction outcomes could be classified as tolerated or deleterious.

2.5. I-Mutant3.0

(http://gpcr2.biocomp.unibo.it/cgi/predictors/I-Mutant3.0/I-Mutant3.0.cgi For studying the effect of mutations on protein Stability. I- Mutant3.0 software was used.). It is a neural network based tool, predicts the change in the stability of the protein upon mutation [10]. The output is obtained in the form of protein stability change upon mutation and Gibbs-free energy change (DDG) either increased or decreased stability.

2.6. Project Hope

(http://www.cmbi.ru.nl/hope/). It is an automatic program that analyzes the structural and functional effects of point mutations. Five SNPs were inserted into the software and the results shows the effect of the mutation in the amino acid properties and how this affects the also plus an image for protein structure is displayed whenever available [10].

2.7. SNPs &GO (Single Nucleotide Polymorphism &Gene Ontology), PHD-SNP

(http://snps.biofold.org/snps-and-go) [2]. SNPs& GO is an accurate method that, starting from a protein sequence, can predict whether a variation is disease related or not by exploiting the corresponding protein functional annotation. SNPs& GO collects in unique framework information derived from protein sequence, evolutionary information, and function as encoded in the Gene Ontology terms, and outperforms other available predictive methods. [2] The protein sequences is submitted in FASTA format that is obtained from UniprotKB / ExPASY after submitting the sequence the mutations were submitted in the XPOSY format where X and Y are the wild-type and mutant residues respectively. The result is shown as Neutral or disease. PHD-SNP results are presented as part of SNPs& GO output

3. Results

In this study *AGT* gene was found to have an association with 20 other different genes. Among them the most important one is *REN* (responsible for production of renin in the kidney) and *AGTR2* (responsible for encoding receptor for angiotensin II) (Figure 1 and Table 1). The physical interaction and co expression of this gene with other related gene are shown in figure 1. The genes expressed with *AGT* gene were shown in Table 3, Appendix.

The total number of SNPs obtained was 173 the non-synonymous SNPs that were predicted to be deleterious by mutation were 46 and that not causing damage or tolerated were 127 SNPs using SIFT software. Analysis using Polyphen -2 revealed one SNP as benign, 12 as possibly damaging and 33 are probably damaging. Analysis with provean showed that 19 were neutral and 27 were deleterious. Protein stability was checked using I-mutant software which showsed13 SNPs increasing the protein stability and 33 were decreasing the protein stability. Prediction of whether SNPs were deleterious were checked using PhD-SNP software and showed 20 disease related and 18 were neutral in all SNPs. Also SNPs were checked using SNP & Go software that showed 32 neutral and 14 were disease associated variation. The detailed results for SIFT, Polyphen-2, Provean-2 were shown in Table A1. The detailed results for I-mutant, SNP&GO and PHD.

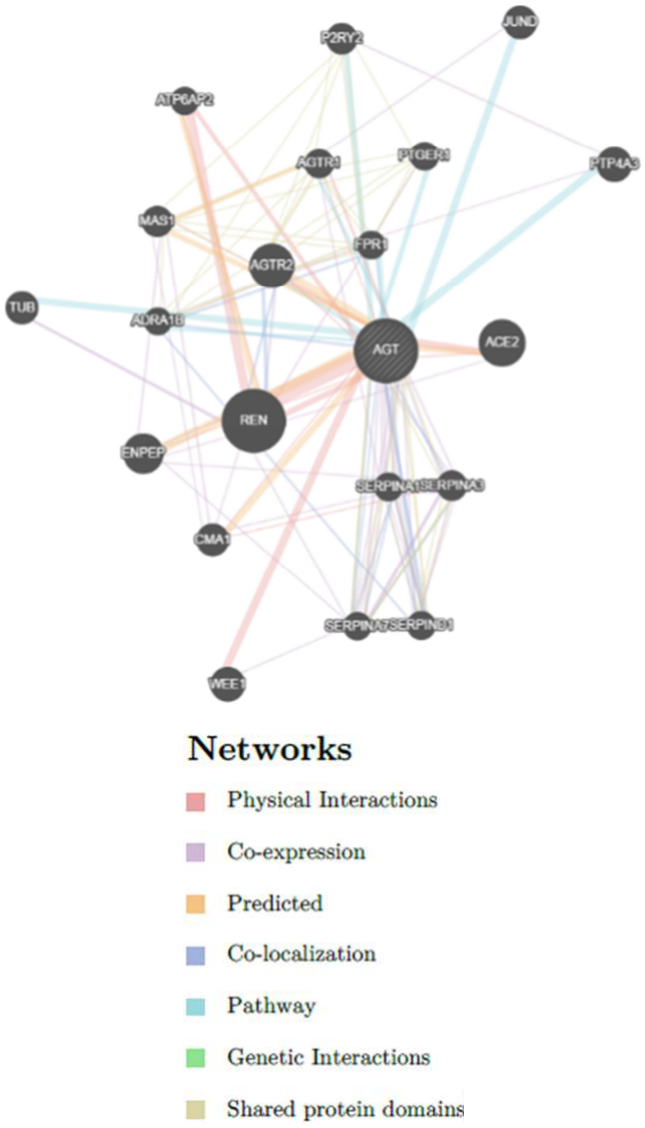

Figure 1. *GeneMANIA result.*

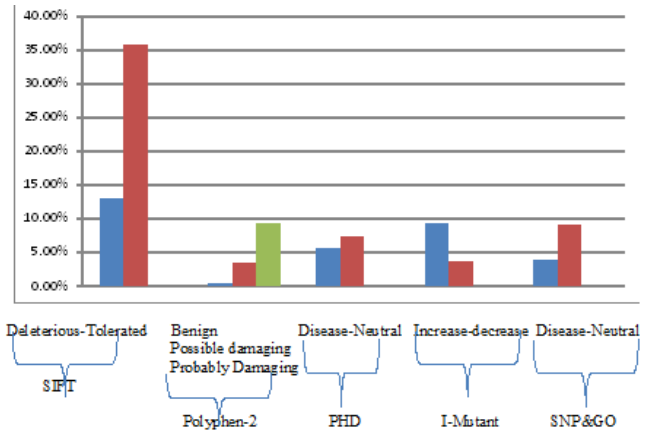

Figure 2. *The results of different software.*

Generally when using the sixth software (SIFT, Polyphen-2, Provean, PhD, I-Mutant and SNP & GO) all were showing abnormal appearance with effect as diseased, 33 SNPs showed decrease in protein stability using I-Mutant software. The structural impact of SNPs and its function was investigated using Project Hope software.

1. rs368513901, Tryptophan into a Arginine at position 261

The mutant residue is smaller than the wild-type residue. This will cause a possible loss of external interactions

The mutant residue is NEUTRAL, the mutant residue charge is POSITIVE. this can cause repulsion between the mutant residue and neighboring residues.

The wild-type residue is more hydrophobic than the mutant residue. The mutation might cause loss of hydrophobic interactions with other molecules on the surface of the protein.

2. rs137858911, Isoleucine into a Serine at position 345

The mutant residue is smaller than the wild-type residue. The mutation will cause an empty space in the core of the protein.

The wild-type residue is very conserved, but a few other residue types have been observed at this position too.

The wild-type residue is more hydrophobic than the mutant residue. The mutation will cause loss of hydrophobic interactions in the core of the protein.

3. rs137858911, Isoleucine into a Serine at position 345.

The mutant residue is smaller than the wild-type residue.

The mutation will cause an empty space in the core of the protein.

The hydrophobicity of the wild-type and mutant residue differs.

The mutation will cause loss of hydrophobic interactions in the core of the protein

4. rs375261929, Arginine into a Cysteine at position 458.

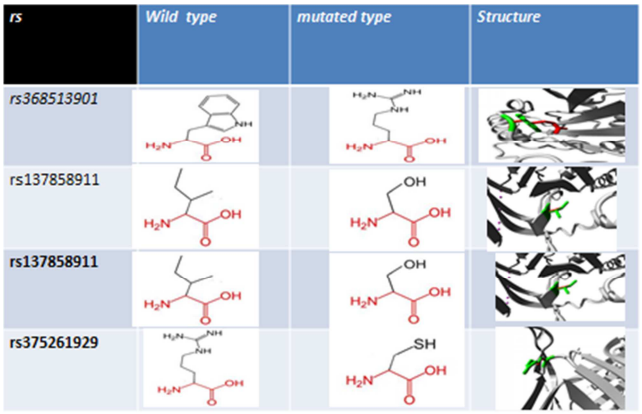

Figure 3. *Project Hope results.*

The mutant residue is smaller than the wild-type residue. The wild-type residue forms a hydrogen bond with Proline at position 347. The size difference between wild-type and mutant residue makes that the new residue is not in the correct position to make the same hydrogen bond as the original wild-type residue did.

The wild-type residue charge was POSITIVE, the mutant residue charge is NEUTRAL. The difference in charge will disturb the ionic interaction made by the original, wild-type residue.

The mutant residue is more hydrophobic than the wild-

type residue. The difference in hydrophobicity will affect hydrogen bond formation. The wild-type residue forms a salt bridge with Aspartic Acid at position 352.

Results were shown in Figure 3.

4. Discussion

In this study all the 14 nsSNPs showed a damaging effect and disease related condition (rs143545998 (G29D), rs61731497 (C51R), rs2229389 (G114C), rs141302625 (L219Q), rs61762537 (R237C), rs145882750 (R237L), rs3685139 (W261R), rs56073403 (Y281C), rs147736976 (I345S), rs201501261 (P347L), rs137858911 (M381R), rs61762527 (P382A), rs375261929 (R458C), rs143479528 (P481L)). Five nsSNPs (rs61731497 (C51R), rs2229389 (G114C), rs61762537 (R237C) rs56073403 (Y281C) and rs61762527 (P382A), found in this study were also reported in another study as deleterious and causing disease in *AGT* gene analysis using computational approach [12]. Also five nsSNPs (rs143545998 (G29D), rs141302625 (L219Q), rs145882750 (R237L), rs201501261 (P347L), and rs143479528 (P481L), were found to be deleterious in *AGT* gene analysis [13]. The four remaining nsSNPs (rs368513901 (W261R), rs137858911 (M381R), rs147736976 (I345S) and rs375261929 (R458C) were reported in this study for the first time. The dominant clinical investigation was hypertension (NCBI) followed by renal tubular dysgenesis and eclampsia in human and mainly affecting the protein.

5. Conclusions

In conclusion, extensive functional and structural analyses are carried out to predict potentially damaging and deleterious nsSNPs of *AGT* gene using bioinformatics and computational methods. In the study, 14 high confidence damaging nsSNPs are identified from 172 nsSNPs. Although bioinformatics tools have their limitations, the results from the present study may be convenient in future for further population based research activities and towards development of accuracy medicines.

6. Recommendations

SNPs in *AGT* gene cause may diseases mainly hypertension and other related diseases for the fact that hypertension is a main chronic disease worldwide. More wet-lab research regarding these 14 SNPs is recommended. The SNPs in the non-coding region also needs to be considere

Appendix

Table A1. *SIFT, Provean and Polyphen-2 results.*

SNP	SIFT prediction	Provean score	Provean prediction	Polyphen-2 score	Polyphen-2 result
rs4762	Deleterious	-3.477	Deleterious	1	Probably Damaging
rs5041	Deleterious	0.157	Neutral	0.582	Possibly Damaging
rs1805090	Deleterious	-1.098	Neutral	0.852	Possibly Damaging
rs2229389	Deleterious	-6.401	Deleterious	1	Probably Damaging
rs11557882	Deleterious	-1.572	Neutral	1	Probably Damaging
rs11557883	Deleterious	-3.898	Deleterious	0.55	Possibly Damaging
rs11568032	Deleterious	-1.411	Neutral	1	Probably Damaging
rs17856352	Deleterious	-6.039	Deleterious	0.685	Possibly Damaging
rs56073403	Deleterious	-5.712	Deleterious	1	Probably Damaging
rs61731497	Deleterious	-7.334	Deleterious	1	Probably Damaging
rs61751065	Deleterious	-590	Neutral	1	Probably Damaging
rs61751067	Deleterious	-1.776	Neutral	0.31	Benign
rs61751076	Deleterious	-1.771	Neutral	1	Probably Damaging
rs61751077	Deleterious	-2.798	Deleterious	0.998	Probably Damaging
rs61762527	Deleterious	-7.358	Deleterious	0.996	Probably Damaging
rs61762537	Deleterious	-5.296	Deleterious	1	Probably Damaging
rs74315283	Deleterious	-2.032	Neutral	1	Probably Damaging
rs137858911	Deleterious	-3.907	Deleterious	1	Probably Damaging
rs140964843	Deleterious	-1.747	Neutral	0.997	Probably Damaging
rs141302625	Deleterious	-5.332	Deleterious	0.975	Probably Damaging
rs141724549	Deleterious	-2.002	Neutral	1	Probably Damaging
rs143437550	Deleterious	-7.37	Deleterious	0.988	Probably Damaging
rs143479528	Deleterious	-7.37	Deleterious	1	Probably Damaging
rs143545998	Deleterious	-2.036	Neutral	1	Probably Damaging
rs145882750	Deleterious	-4.605	Deleterious	0.961	Probably Damaging
rs146284519	Deleterious	-4.053	Deleterious	1	Probably Damaging
rs146566988	Deleterious	-2.161	Neutral	1	Probably Damaging
rs147355405	Deleterious	-5.212	Deleterious	0.818	Possibly Damaging
rs147736976	Deleterious	-4.98	Deleterious	1	Probably Damaging
rs149236456	Deleterious	-1.452	Neutral	0.998	Probably Damaging

SNP	SIFT prediction	Provean score	Provean prediction	Polyphen-2 score	Polyphen-2 result
rs149973083	Deleterious	-1.102	Neutral	0.587	Possibly Damaging
rs150161533	Deleterious	-2.056	Neutral	0.799	Possibly Damaging
rs151194891	Deleterious	0.328	Neutral	0.998	Probably Damaging
rs199817559	Deleterious	-0.666	Neutral	0.779	Possibly Damaging
rs199864970	Deleterious	-1.736	Neutral	0.648	Possibly Damaging
rs200712921	Deleterious	-2.908	Deleterious	0.997	Probably Damaging
rs201162475	Deleterious	-4.925	Deleterious	0.297	Benign
rs201352496	Deleterious	-2.638	Deleterious	1	Probably Damaging
rs201501261	Deleterious	-7.992	Deleterious	0.994	Probably Damaging
rs201569036	Deleterious	-1.366	Neutral	1	Probably Damaging
rs267598410	Deleterious	-3.579	Deleterious	0.603	Possibly Damaging
rs368513901	Deleterious	-3.579	Deleterious	1	Probably Damaging
rs369727853	Deleterious	-3.302	Deleterious	0.999	Probably Damaging
rs374407232	Deleterious	-0.307	Neutral	0.998	Probably Damaging
rs374540090	Deleterious	-3.019	Deleterious	0.824	Possibly Damaging
rs375261929	Deleterious	-4.844	Deleterious	0.982	Probably Damaging

Table A2. *I-mutant, SNP& GO and PHD results.*

SNP	RI	I- mutant result	SNP& GO	PHD
rs4762	5	Decrease	neutral	Neutral
rs5041	7	Decrease	neutral	Disease
rs1805090	1	Decrease	neutral	Neutral
rs2229389	5	Decrease	disease	disease
rs11557882	4	Decrease	neutral	neutral
rs11557883	8	Decrease	neutral	neutral
rs11568032	9	Decrease	neutral	disease
rs17856352	7	Increase	neutral	neutral
rs56073403	4	Decrease	disease	disease
rs61731497	5	Increase	disease	disease
rs61751065	2	Decrease	Neutral	neutral
rs61751067	3	Increase	Neutral	disease
rs61751076	0	Increase	Neutral	neutral
rs61751077	1	Decrease	Neutral	neutral
rs61762527	8	Decrease	Disease	disease
rs61762537	1	Increase	Disease	disease
rs74315283	6	Decrease	Neutral	neutral
rs137858911	3	Decrease	Disease	disease
rs140964843	7	Decrease	Neutral	neutral
rs141302625	4	Decrease	Disease	disease
rs141724549	5	Increase	Neutral	disease
rs143437550	7	Decrease	Neutral	neutral
rs143479528	5	Increase	Disease	disease
rs143545998	7	Decrease	Disease	disease
rs145882750	2	Increase	Disease	disease
rs146284519	5	Decrease	Neutral	disease
rs146566988	2	Increase	Neutral	neutral
rs147355405	1	Increase	Neutral	disease
rs147736976	10	Decrease	Disease	disease
rs149236456	5	Decrease	Neutral	disease
rs149973083	9	Decrease	Neutral	neutral
rs150161533	8	Decrease	Neutral	neutral
rs151194891	9	Decrease	Neutral	neutral
rs199817559	6	Decrease	Neutral	disease
rs199864970	4	Decrease	Neutral	disease
rs200712921	1	Decrease	Neutral	disease
rs201162475	2	Decrease	Neutral	disease
rs201352496	8	Decrease	Neutral	disease
rs201501261	2	Increase	Disease	disease
rs201569036	2	Increase	Neutral	neutral
rs267598410	2	Increase	Neutral	disease
rs368513901	2	Decrease	Disease	disease
rs369727853	5	Decrease	Neutral	neutral
rs374407232	8	Decrease	Neutral	neutral
rs374540090	7	Decrease	Neutral	Disease
rs375261929	5	Decrease	Disease	Disease

Gene	Description	Rank
AGT	angiotensinogen [Source:HGNC Symbol;Acc:HGNC:333]	N/A
REN	renin [Source:HGNC Symbol;Acc:HGNC:9958]	1
ACE2	angiotensin I converting enzyme 2 [Source:HGNC Symbol;Acc:HGNC:13557]	2
AGTR2	angiotensin II receptor type 2 [Source:HGNC Symbol;Acc:HGNC:338]	3
ENPEP	glutamyl aminopeptidase [Source:HGNC Symbol;Acc:HGNC:3355]	4
PTP4A3	protein tyrosine phosphatase type IVA, member 3 [Source:HGNC Symbol;Acc:HGNC:9636]	5
WEE1	WEE1 G2 checkpoint kinase [Source:HGNC Symbol;Acc:HGNC:12761]	6
JUND	JunD proto-oncogene, AP-1 transcription factor subunit [Source:HGNC Symbol;Acc:HGNC:6206]	7
TUB	tubby bipartite transcription factor [Source:HGNC Symbol;Acc:HGNC:12406]	8
CMA1	chymase 1 [Source:HGNC Symbol;Acc:HGNC:2097]	9
P2RY2	purinergic receptor P2Y2 [Source:HGNC Symbol;Acc:HGNC:8541]	10
MAS1	MAS1 proto-oncogene, G protein-coupled receptor [Source:HGNC Symbol;Acc:HGNC:6899]	11
SERPINA3	serpin family A member 3 [Source:HGNC Symbol;Acc:HGNC:16]	12
AGTR1	angiotensin II receptor type 1 [Source:HGNC Symbol;Acc:HGNC:336]	13
PTGER1	prostaglandin E receptor 1 [Source:HGNC Symbol;Acc:HGNC:9593]	14
SERPIND1	serpin family D member 1 [Source:HGNC Symbol;Acc:HGNC:4838]	15
FPR1	formyl peptide receptor 1 [Source:HGNC Symbol;Acc:HGNC:3826]	16
SERPINA1	serpin family A member 1 [Source:HGNC Symbol;Acc:HGNC:8941]	17
SERPINA7	serpin family A member 7 [Source:HGNC Symbol;Acc:HGNC:11583]	18
ATP6AP2	ATPase H+ transporting accessory protein 2 [Source:HGNC Symbol;Acc:HGNC:18305]	19
ADRA1B	adrenoceptor alpha 1B [Source:HGNC Symbol;Acc:HGNC:278]	20

Figure A1. *Genes co-expressed with AGT gene using GeneMANIA software.*

Table A3. *I-mutant, SNP& GO and PHD results.*

Amino acid change	SNPs	Status	I-Mutant RI	I- Mutant result	SNPs& GO	PHD SNP
G29D	rs143545998	Reported	7	decrease	Disease	disease
C51R	rs61731497	Reported	5	increase	Disease	disease
G114C	rs2229389	Reported	5	decrease	Disease	disease
L219Q	rs141302625	Reported	4	decrease	Disease	disease
R237C	rs61762537	Reported	1	increase	Disease	disease
R237L	rs145882750	Reported	2	increase	Disease	disease
W261R	rs368513901	Novel	2	decrease	Disease	disease
Y281C	rs56073403	Reported	4	decrease	Disease	disease
I345S	rs147736976	Novel	10	decrease	Disease	disease
P347L	rs201501261	Reported	2	increase	Disease	disease
M381R	rs137858911	Novel	3	decrease	Disease	disease
P382A	rs61762527	Reported	8	decrease	Disease	disease
R458C	rs375261929	Novel	5	decrease	Disease	disease
P481L	rs143479528	Reported	5	increase	Disease	disease

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