II. GENETİKA və GENOMİKA | GENETICS and GENOMICS

UOT 577.21; 577.214; 577.214.43

INTER-SPECIES CONSERVATION OF THE AGT AND AGTR1 GENES PROMOTERS IN HUMANS AND SOME OTHER PRIMATES

ZUMRUD ABASZADE[1], AYSEL ALIYEVA[2], LALA MAMMADOVA[2], ILHAM SHAHMURADOV[2,3*]

[1] Azerbaijan Medical University, Baku, AZ 1022, 23, A.A. Bakikhanov str.
[2]Institute of Biophysics, Ministry of Science and Education of the Republic of Azerbaijan, 117, Z. Khalilov str., AZ 1141, Baku, Azerbaijan
[3]Genetic Resources Institute, Ministry of Science and Education of the Republic of Azerbaijan, 155, Azadlig ave, AZ 1106, Baku, Azerbaijan
ilhambaku@gmail.com

A computer analysis of the inter-species conservation peculiarities of the AGT and AGTR1 gene promoters in 8 primate species, as human (*Homo sapiens*), gorilla (*Gorilla gorilla*), chimpanzee (*Pan troglodytes*), anubis baboon (*Papio anubis*), Tibetan macaque (*Macaca thibetana*), rhesus macaque (*Macaca mulatta*), crab-eating *Macaca fascicularis* and common marmoset (*Callithrix jacchus*). It was found that although some block rearrangements have occurred in the promoter regions both of AGT and AGTR1 genes of these species during evolution, the promoter nucleotide sequences show very high (≥85%) similarity. To evaluate a level of the inter-species conservation of some transcription factor binding sites (TFBSs) in the AGT and AGTR1 promoters, a search for TFBS motifs available in promoter all or most of these genes from these species was carried out. It was revealed that only a single TFBS (p53 binding site) motif is available in the AGT promoter all of these species. However, in the case of the AGTR1 gene promoter, it was found to be more conservative. Thus, the AGTR1 gene promoter from each of the 8 species contains motifs of Sp1, Sp2, Sp3, EGR-1 and MAZ binding sites. According to the results, it can be assumed that the regulatory mechanisms of the transcription of the AGTR1 genes in the studied species, compared to the AGT gene, have been relatively less modified during ten million years of evolution. In this work, we also explored a role of TFs/TFBSs in the coordinated expression of the functionally related group of AH-related genes. For this purpose, we carried out a comparison of the TFBS content of 12 AH-related genes. Only motifs of a few TFBSs were found to be available in most of AH-genes, including Sp1 binding element.

Keywords: *arterial hypertension, AGT gene, AGTR1 gene, promoter, transcription factors, promoter analysis*

INTRODUCTION

Arterial hypertension (AH) is one of the main causes of cardiovascular diseases. It has both genetic and non-genetic causes (Kunutsor and Powles, 2010; Nguyen and Jaisser, 2012; Jordan, Kurschat and Reuter, 2018). To date, more than 40 genes associated with AH have been identified (Austin and Loyd, 2014; Garcia-Rivas et al, 2017; https://www.omim.org/entry/145500). Some of these genes are listed in Table 1.

AGT (Caulfield et al., 1994; Lifton, 1996) and AGTR1 (Bonnardeaux et al., 1994) genes are among the most studied genes known to be associated with AH.

The AGT gene encodes the angiotensinogen protein (485 amino acids), a precursor of the angiotensin II protein which is the substrate of the renin protein, First, the signal peptide, then after the peptide bond between Leu and Val amino acids is cut by renin, angiotensin II is converted to the

https://doi.org/10.61642/202415
Available online 26 December 2024

10-amino acid (aa) peptide hormone of angiotensin I (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu) After that, the ACE enzyme converts that peptide into the (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe) angiotensin II peptide The AGT gene is expressed mainly in the liver (hepatocytes) (Lifton, 1996; Ferreira and Raizada, 2008; Lu et al., 2016; Wu et al., 2018; Chappell, 2019). The AGT gene is located on the chromosome 1 (see: Table 1). Two partially different mRNAs are created as a result of the transcription initiation of the AGT gene from alternative transcription start sites (TSS #1 [v1]: 230745583; TSS #2 [v2]: 230714122). But, the coding DNA sequence (CDS) for these mRNAs is the same (https://www.genecards.org/cgi-bin/carddisp.pl?gene=AGT&keywords=AGT; NC_000001.11).

The AGTR1 gene encodes the angiotensin II protein type I receptor. It is located on the chromosome 3 (see: Table 1). Only one transcription start site (TSS: 148697903) is known for the AGTR1 gene, but an alternative splicing produces 7 different mRNAs, although all of these mRNAs encode the same CDS (https://www.genecards.org/cgi-bin/carddisp.pl?gene=AGTR1; NC_000003.12).

Table 1.

List of some hypertension-related genes of human

Gene name	**Gene product**	**Gene localization***	**References**
AGT	Angiotensinogen/angiotensin	Chromosome 1, c(230702523..230745583) **	Caulfield et al., 1994; Lifton, 1996; Lu et al., 2016; Wu et al., 2018
AGTR1	Angiotensin II protein type I receptor	Chromosome 3, 148697903..148743003	Bonnardeaux et al., 1994
ACE	Angiotensin-converting enzyme	Chromososme 17, 63477061..63498380	Puthucheary et al., 2011
REN	Renin (angiotensinogenase)	Chromosome 1, c(204154816..204166337)	Miyazaki et al., 1984
MTHFR	Methylenetetrahydrofolate reductase	Chromosome 1, c(11785730..11806103)	Homberger et al., 2000
ITGB3	β3 subunit of a receptor protein (integrin alphaIIb/beta3	Chromosome 17, 47253842..47312711	Weiss et al., 2004
CBS	Cystathionine β-synthase	Chromososme 21, c(43053190..43076861)	Kraus et al., 1998
FGB	Fibrinogen beta chain	Chromosome 4, 154562980..154572763	Fish, 2012
F2	Coagulation factor II (Prothrombin,)	Chromososme 11, 46719166..46739508	Chinnaraj, Planer and Pozi, 2018
F5	Coagulation factor V	Chromosome 1, c(169511954..169586630)	Vossen et al., 2007
F7	Coagulation factor VII	Chromosome 13, 113105773..113120681	Vossen et al., 2007
F13A1	Coagulation factor XIIIa	|Chromosome 6, c(6144078..6320691)	*Achyuthan et al., 1996*

* https://www.ncbi.nlm.nih.gov/datasets/genome/GCF_000001405.38/ (the human genome assembly, release GRCh38.p12); ** 'c' means complement.

The critical players in the control of transcription, the first crucial step in gene expression, are transcription factors (TFs) and their binding sites (TFBS) on DNA. TFBSs are mostly localized in

proximal and distal promoter regions. The length of TFBSs varies mostly from 5 to 15 base pairs (bp) of length (Woychik and Hampsey, 2002; Butler et al., 2002; Smale and Kadonaga, 2003; Hahn, 2004; Juven-Gershon, et al., 2008; Solovyev, Shahmuradov and Salamov, 2010; Schier and Taatjes, 2020). TFBSs may act in a species- and/or tissue-specific manner. Moreover, an activity of and TFBSs may be depend on intra- and inter-sell siginals, enviromantal conditions.

Identification of functional TFBSs in the promoter region of that gene is extremely important for understanding the mechanisms of transcriptional regulation of the expression of any gene. Functional TFBSs can be revealed either (1) directly experimentally or (2) initially by *in silico* analysis and only then by experimental verification. The first way, which is the most accurate, requires more financial/human resources. Moreover, not all TFBS can be directly identified by experimental methods. Another way (*in silico* + experiment) is to first find statistically non-random motifs of known TFBSs in the promoter region of the studied gene, and then check whether those motifs are conserved at least in the same gene of other species of primates are evolutionarily/taxonomically close. Here, conservative TFBS-motives are expected to be functional.

Primates fall into two distinct subcategories: (1) monkeys (New-World and Old-World), and (2) apes (great Apes as orangutans, gorillas, chimpanzees and humans, and lesser apes) (Doolittle et al., 1996; Chen and Li, 2001; Glazko and Nei, 2003; Rogers and Gibbs, 2014; Easteal and Herbert, 1997). The gorilla (*Gorilla gorilla*) and chimpanzee (*Pan troglodytes*) are species of primate from the ape family. The anubis baboon (*Papio anubis*) is a species of primate in the family Cercopithecidae. The Tibetan macaque (*Macaca thibetana*) is a macaque native to eastern Tibet east to Guangdong and north to Shaanxi in China. The rhesus macaque (*Macaca mulatta*) is a species of macaque, one of the most famous species of the monkey family. The crab-eating *Macaca fascicularis*, as well as *M.mulatta*, the common marmoset (*Callithrix jacchus*) are non-human primates (Glazko and Nei, 2003; Rogers and Gibbs, 2014; Arnason, Gullberg and Janke, 1998).

The times of divergence of the primate lineages are still controversial (Doolittle et al., 1996; Chen and Li, 2001; Glazko and Nei, 2003). For example, the estimate of the time of divergence between humans and chimpanzees varies from 3.6 MYA (Easteal and Herbert, 1997) to 13 MYA (Arnason, Gullberg and Janke, 1998). Chimpanzees are the closest living relatives of humans. Later, it was suggested that the ancestors of today's humans and chimps went their separate ways about 4 million to 6 million years ago, and the ancestors of gorillas diverged about 7 million to 9 million years ago. The divergence of human and rhesus macaque lineages is more confidently dated at 25–28 million years ago (Rogers and Gibbs, 2014). The human–chimpanzee sequence divergence is estimated at 1.1–1.4%. The humans and gorillas share more than 96% of their genomes. The human and olive baboon share about 94% of their genomes (Batra et al., 2020). The human and *M.fascicularis* share more than 92% of their genomes (Ebeling et al., 2011). The majority of protein-coding genes have 1:1 homologue among humans, the great apes and Old-World monkeys sequenced to date, but gene content is not identical among species. The difference in single copy sequence between human and rhesus macaque is approximately 6.5% (Rogers and Gibbs, 2014).

In this study, we performed (1) the inter-species BLAST comparison of promoter sequences and (2) a search for inter-species conservative TFBS motifs in promoters of AGT and AGTR1 genes in humans and seven other primates (monkeys and apes). Besides, we tried to identify intra-species conservative TFBS motifs in the human 12 genes associated with AH, including AGT and AGTR1. Results of these studies are explained below.

MATERIALS and METHODS

The nucleotide sequences of [-1000+100] regions of AGT and AGTR1 genes of 8 primates were taken from the corresponding genome annotations. AGT gene: chimpanzee - NC_072398.1, Chr1:c(212839081..212850067); gorilla - NC_073224.1, Chr1:229040553.. 229051589; rhesus macaque - NC_041754.1, Chr1:18283971..18296759; crab-eating macaque - NC_052255.1, Chr1:18191836..18253210; Tibetan macaque - NC_065578.1, Chr1: c(202197606..202209270); common marmoset - NC_071460.1, Chr19: 16115525..16130738; olive baboon - NC_044976.1, Chr1:c(200114352..200126770). AGTR1 gene: chimpanzee - NC_072401.1, Chr3:151805290..

151850128; gorilla - NC_073227.1, Chr3:159715041..159759942; Rhesus macaque - NC_041755.1, Chr2:50825360..50870238; crab-eating macaque - NC_052256.1, Chr2:c(143213541..143258339); Tibetan macaque - NC_065579.1, Chr2:51188797..51233660; common marmoset - NC_071458.1, Chr17: c(29551838..29595986); olive baboon - NC_044977.1, Chr2:c(143193353..143238129). For the human AGT and AGTR1 genes see above. Hereinafter the +1 position corresponds to the annotated start of a gene.

For the AGT gene, two different regions of [-1000+100] were taken according to the alternative gene start points (v1 and v2) mentioned above.

Comparison of promoter and protein sequences were performed by the BLAST tool (Altschul et al., 1997). A search for statistically non-random motifs of known 652 TFBS from RegsiteDB (http://www.softberry.com/berry.phtml?topic=regsitelist) was performed by the **Nsite** tool (Shahmuradov and Solovyev, 2015). All bioinformatics analyzes were performed on the LINUX operating system.

RESULTS and DISCUSSION

Comparison of promoter regions of the AGT and AGTR1 genes from 8 primate species

First, using the BLASTN program, the human AGT and AGTR1 genes nucleotide sequences of [-1000:+100] regions were pairwise compared with promoter sequences of corresponding genes of other 7 primate species. In addition, human AGT and AGTR1 protein sequences were compared with protein sequences of other species using BLASTP program. The results of this comparison are shown in Tables 2 and 3, Figures 1 and 2.

Table 2.

Similarity regions between the promoter regions of some primate AGT genes[1].

Compared Species	Protein Length, aa[1]	Similarity Region	Identities	Similarity Level, %	Gaps
Hs *vs* Pt	485^{Pt}	Protein: 1-476^{Hs}, 10-485^{Pt} Promoter: 2-1100^{Hs}, 1-1099^{Pt}	472 1088	99 99	0 0
Hs *vs* Gg	485^{Gg}	Protein: 1-476^{Hs}, 10-485^{Gg} Promoter: 10-1100^{Hs}, 8-1098^{Gg}	473 1076	99 99	0 0
Hs *vs* Pa	490^{Pa}	Protein: 1-476^{Hs}, 15-490^{Pa} Promoter: 350-1100^{Hs}, 338-1094^{Pa}	440 707	92 93	0 14
Hs *vs* Mf	490^{Mf}	Protein: 1-476^{Hs}, 15-490^{Mf} Promoter: 350-1100^{Hs}, 344-1100^{Mf}	439 702	92 92	0 14
Hs *vs* Mt	490^{Mt}	Protein: 1-476^{Hs}, 15-490^{Mt} Promoter: 350-1068^{Hs}, 374-1098^{Mt}	439 676	92 93	0 14
Hs *vs* Mm	490^{Mm}	Protein: 1-476^{Hs}, 15-490^{Mm} Promoter: 350-623^{Hs}, 817-1100^{Mm}	440 261	92 92	0 10
Hs *vs* Cj	491^{Cj}	Protein: 1-475^{Hs}, 15-490^{Cj} Promoter: 349-625^{Hs}, 821-1100^{Cj}	413 240	87 85	1 9

[1]Hereinafter: Hs – *Homo sapiens*, Gg – *Gorilla gorilla*, Pt – *Pan troglodytes*, Pa – *Papio anubis*, Mf – *Macaca fascicularis*, Mt – *Macaca thibetana*, Mm – *Macaca mulatta*, Cj – *Callithrix jacchus*.

This comparison shows that although some architectural changes (block rearrangements) have occurred in the promoter regions both of AGT and AGTR1 genes, the promoter nucleotide

sequences have very high (≥85%) similarity. Therefore, we can suggest that many TFBS seem to be conserved in promoters both of AGT and AGTR1 genes.

Table 3.

Similarity regions between the promoter regions of some primate AGTR1 genes.

Compared Species	**Protein Length, aa[1]**	**Similarity Region**	**Identities**	**Similarity Level, %**	**Gaps**
Hs *vs* Pt	376^{Pt}	Protein: $1\text{-}359^{Hs}$, $18\text{-}376^{Pt}$ Promoter: $1\text{-}1079^{Hs}$, $19\text{-}1100^{Pt}$	358 1072	99 99	0 3
Hs *vs* Gg	359^{Gg}	Protein: $1\text{-}359^{Hs}$, $1\text{-}359^{Gg}$ Promoter: $1\text{-}981^{Hs}$, $119\text{-}1100^{Gg}$	358 968	99 98	0 3
Hs *vs* Pa	359^{Pa}	Protein: $1\text{-}359^{Hs}$, $1\text{-}359^{Pa}$ Promoter: $276\text{-}1100^{Hs}$, $132\text{-}964^{Pa}$	354 790	99 95	0 8
Hs *vs* Mf	414^{Mf}	Protein: $1\text{-}359^{Hs}$, $56\text{-}414^{Mf}$ Promoter: $52\text{-}350^{Hs}$, $15\text{-}301^{Mf}$ $327\text{-}1098^{Hs}$, $328\text{-}1100^{Mf}$	355 276 735	99 92 95	0 12 5
Hs *vs* Mt	359^{Mt}	Protein: $1\text{-}359^{Hs}$, $1\text{-}359^{Mt}$ Promoter: $158\text{-}1100^{Hs}$, $1\text{-}968^{Mt}$	355 905	99 93	0 27
Hs *vs* Mm	414^{Mm}	Protein: $1\text{-}359^{Hs}$, $56\text{-}414^{Mm}$ Promoter: $17\text{-}1088^{Hs}$, $7\text{-}1100^{Mm}$	355 1018	99 92	0 46
Hs *vs* Cj	359^{Cj}	Protein: $1\text{-}359^{Hs}$, $1\text{-}359^{Cj}$ Promoter: $53\text{-}325^{Hs}$, $1\text{-}264^{Cj}$ $311\text{-}953^{Hs}$, $457\text{-}1100^{Cj}$	353 239 598	98 88 92	0 9 17

Search for the same TFBS motifs in promoter regions of the AGT and AGTR1 genes from 8 primate species

To evaluate the suggestion on the inter-species conservation some TFBSs in the AGT and AGTR1, we carried out a search for TFBS motifs available in promoter all or most of AGT and AGTR1 genes from these species.

It turned out that only 1 TFBS (p53 binding site) motif is available in the AGT promoter all of these species. Besides, in 7 species (out of 8), the Sp1 binding site motif is also available (Table 4, Fig. 3). In terms of the presence of the same TFS, the promoter of the AGTR1 gene seems to be more conservative. Thus, the AGTR1 gene promoter from each of the 8 species contains motifs of Sp1, Sp2, Sp3, EGR-1 and MAZ binding sites. Moreover, in seven species the AGTR1 gene promoter contains motifs of H4TF1, NF-Y and GATA-1 transcription factors (Table 5, Fig. 4).

According to the results, it can be assumed that the regulatory mechanisms of expression (at least, at the transcription level) of the AGTR1 genes in the studied species, compared to the AGT gene, have been relatively less modified during ten millions years of their evolution.

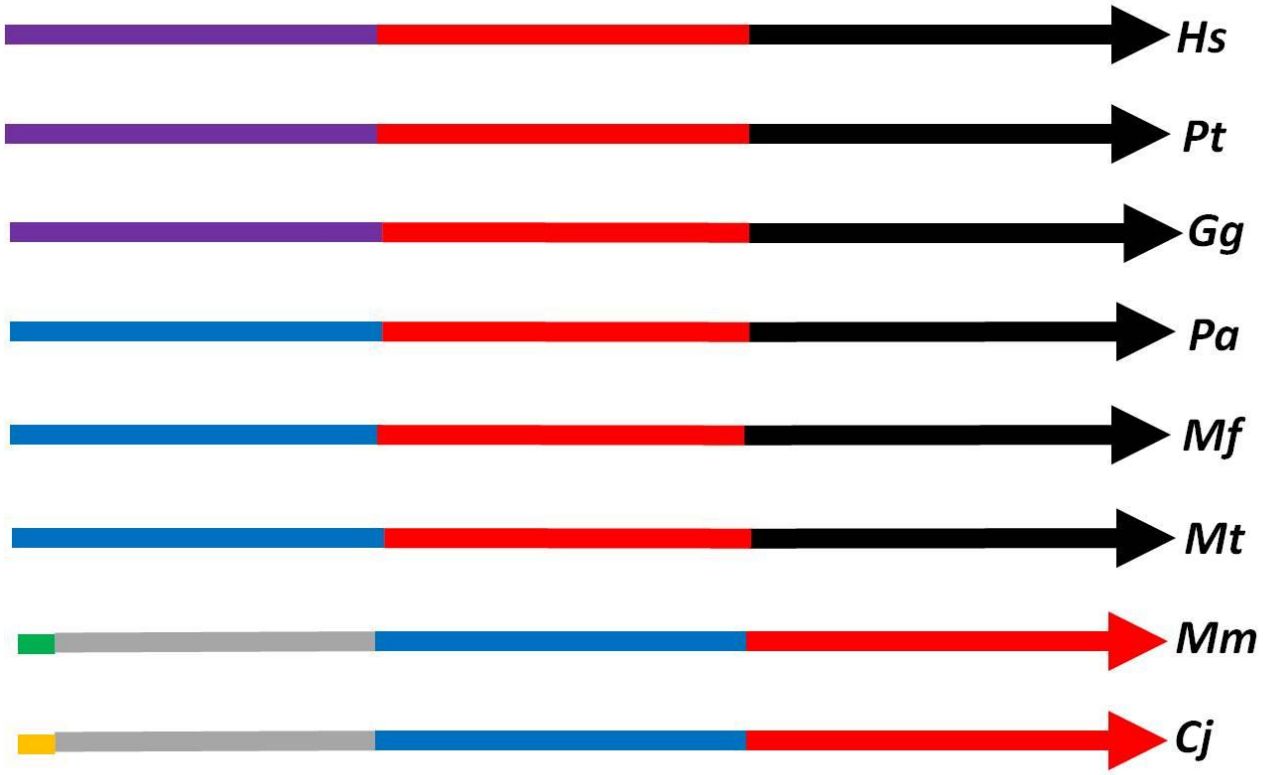

Figure 1. Comparison of promoter regions of some primate AGT genes. Here and in Fig.2, blocks of the sequence similarity between promoters are shown in the same color

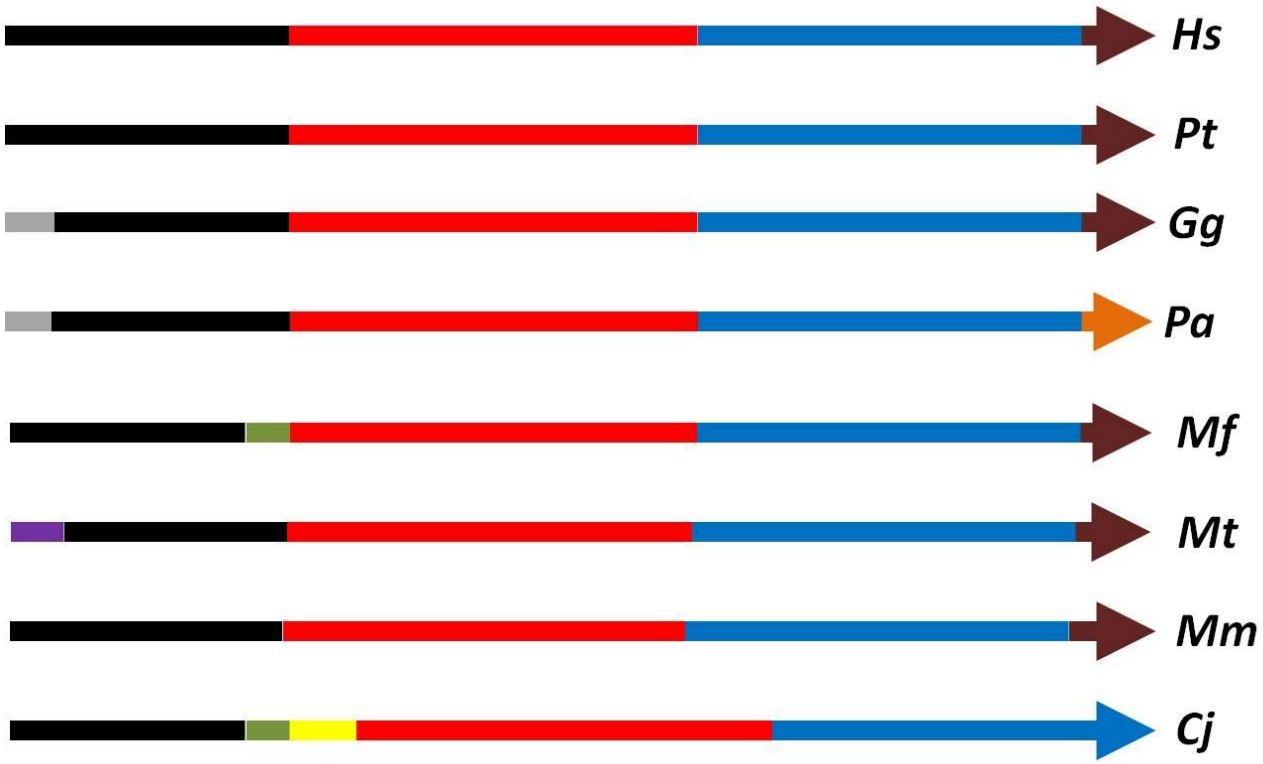

Figure 2. Comparison of promoter regions of some primate AGTR1 genes**.**

Table 3.

Conserved TFBSs in AGT genes of 8 species*

		Transcription Factors										
		p53	Sp1	NF-kappa B	COUP-TFII	MAZ	Fox O1	Ets-1	TEFB	YY1	NF-Y	AP2
Species	Hs	+	+				+	+	+	+	+	+
	Pt	+	+				+	+	+	+	+	+
	Gg	+	+	+			+	+	+	+	+	+
	Mm	+	+	+	+	+						
	Mf	+		+	+	+						
	Mt	+	+	+	+	+						
	Cj	+	+	+	+	+						
	Pa	+	+	+	+	+						

* The “+” sign indicates the presence of the corresponding TFBS motif in the AGT gene of the corresponding species. p53 is a transcription factor that suppresses tumor growth through regulation of dozens of target genes with diverse biological functions (Sullivan et al. (2018). NF-kappaB TFs are the vertebrate orthologs of the Dorsal transcription factor that was originally discovered to be responsible for dorsoventral polarity during the early stages of Drosophila sp. development. The NF-κB members are ubiquitously expressed, but their functionality might depend on specific cellular stimuli (Pires et al., 2018). Myc-associated zinc-finger protein (MAZ) is a transcription factor with dual roles in transcription initiation and termination (Maity et al., 2018). YY1 is a transcription factor that can activate or repress transcription of various genes important in differentiation, development and disease (Stauffer et al., 2015). AP2: The general functions of the AP2 family TFs appear to be the cell-type-specific stimulation of proliferation and the suppression of terminal differentiation during embryonic development (Eckert et al., 2005). Sp1 is a TF of the Sp (Specificity protein) family. It is associated with GC-rich promoters and involved in basal promoter activity (Lu et al., 2023). Nuclear transcription factor Y (NF-Y) is a TF in eukaryotes consisting of three different subunits, NF-YA, NF-YB and NF-YC, which are all necessary for formation of NF-Y complexes and binding to CCAAT boxes in promoters of its target genes (Ly, Yoshida and Yamaguchi, 2013). For other TFBSs see the RegsiteDB (http://www.softberry.com/berry.phtml?topic=regsitelistphtml)

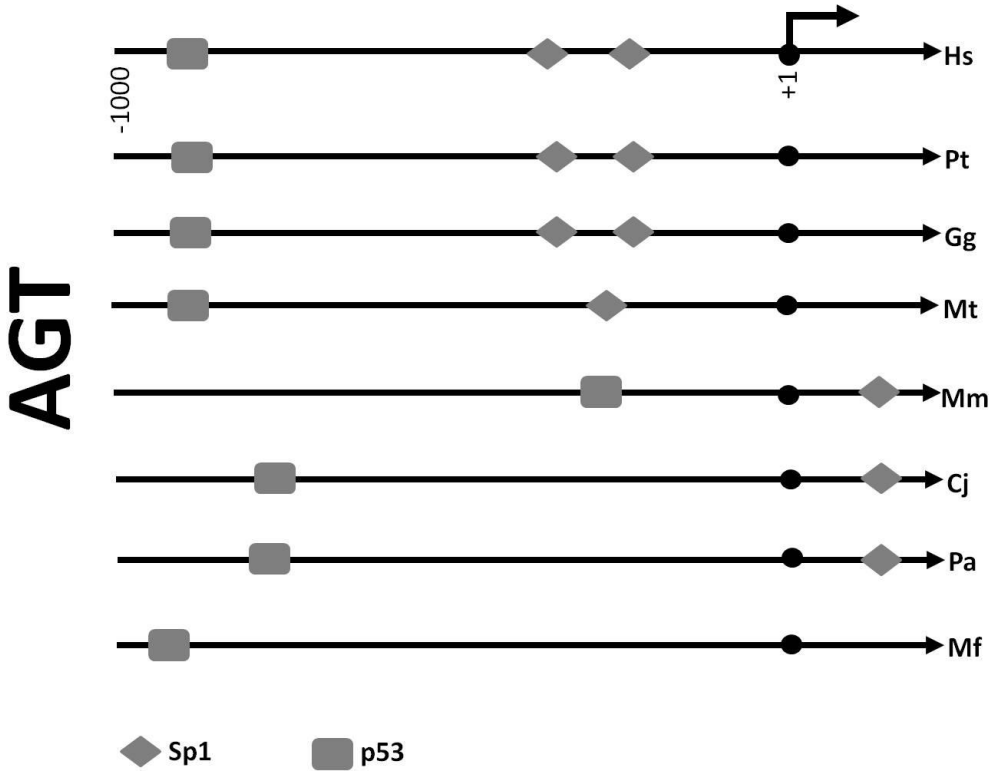

Figure 3. Motifs of the same known TFBS in the promoter region of the AGT gene in all or most species analyzed.

Table 4.

Conserved TFBSs in AGTR1 genes of 8 species *

		Transcription Factors								
		Sp1, Sp2, Sp3	Sp1	Sp1, Sp3	Egr-1, Sp1	MAZ Sp1	H4TF1	NF-Y	Smad3/Smad4	GATA-1
Species	Hs	+	+	+	+	+	+	+	+	+
	Pt	+	+	+	+	+	+	+	+	+
	Gg	+	+	+	+	+	+	+		+
	Mm	+	+	+	+	+	+	+	+	+
	Mf	+	+	+	+	+	+	+	+	+
	Mt	+	+	+	+	+	+	+	+	+
	Cj	+	+	+	+	+	+			
	Pa	+	+	+	+	+		+	+	+

* The "+" sign indicates the presence of the corresponding TFBS motif in the AGTR1 gene of the corresponding species. NF-kappaB TFs are the vertebrate orthologs of the Dorsal transcription

factor that was originally discovered to be responsible for dorsoventral polarity during the early stages of Drosophila sp. development. The NF-κB members are ubiquitously expressed, but their functionality might depend on specific cellular stimuli (Pires et al., 2018). The transcriptional factors of the Sp family of Sp/XKLF transcription factors (Sp1, Sp2, Sp3) are associated with GC-rich promoters and involved in basal promoter activity. Sp2 and Sp3 are members of the Sp subfamily of Sp/XKLF transcription factors (Lu et al., 2023). *Egr-1* is a mammalian transcription factor. It was originally discovered in mice. It is also named as Krox-24, TIS8, and ZENK (Wang et al., 2021). H4TF-1 and H4TF-2 TFs bind specifically to a human histone H4 promoter and activate it (Dailey, Roberts and Heintz, 1987). CRE (cyclic AMP-responsive element) is a binding site of the CREB nuclear transcription factor. CREB regulates genes associated with the neuronal processes, including metabolism and survival and expression of different transcription factors and growth factors (Wang et al., 2018). For a description of other TFBSs see the RegsiteDB.

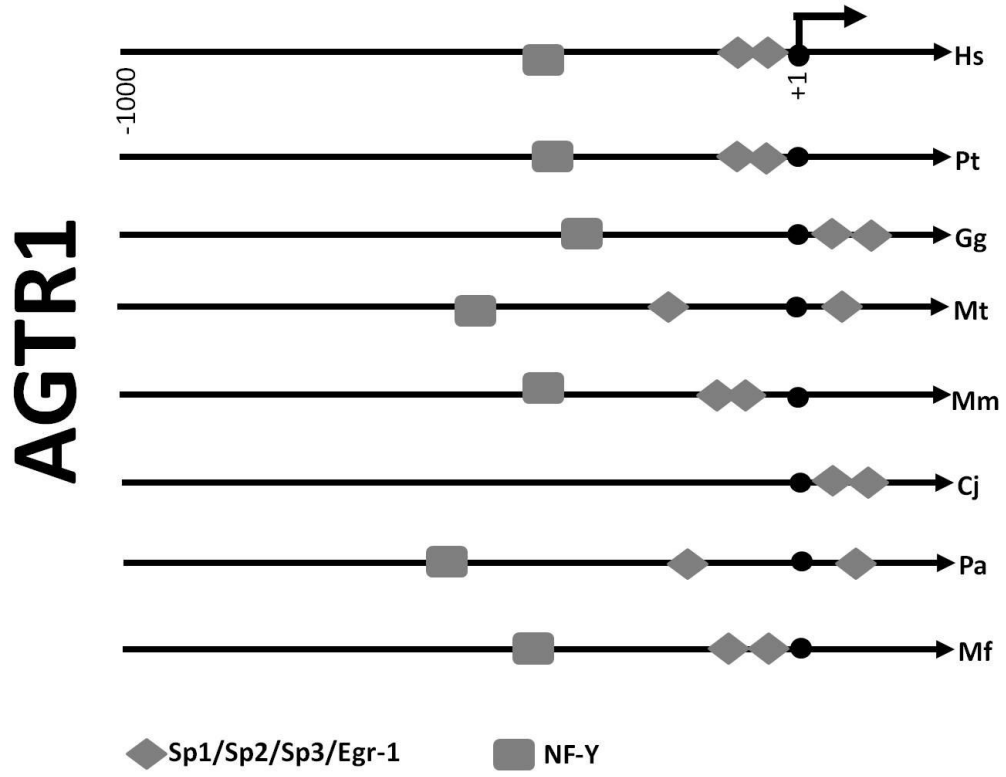

Figure 4. Motifs of the same known TFBS in the promoter region of the AGTR1 gene in all or most species analyzed.

Inter-species comparison the TFBS content of some genes associated with AH

The development and homeostasis of organisms requires the coordinated expression of large sets of genes. One of ways to achieve this goal is positively or negatively coordinated transcription (simultaneously switch on or switch off) via the same TFs/TFBSs (Zinan, Keseroğlu and Özbudak, 2022).

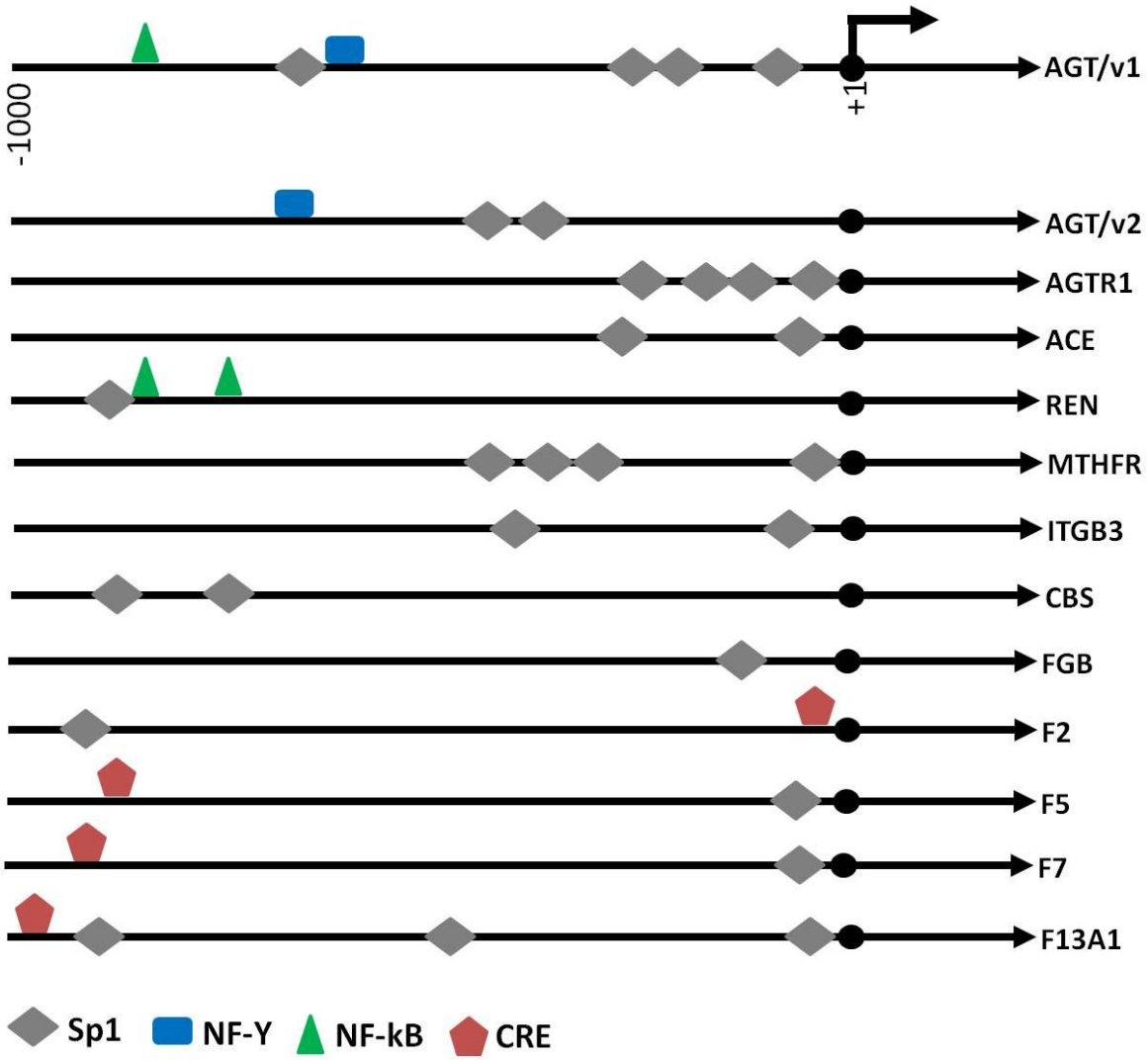

Figure 5. TFBS motifs conserved in genes associated with AH.

Under this work, using the nsiteM program, we carried out a comparison of the TFBS content of 12 genes listed above (Table 1). Results of the comparative analysis are summarized in Fig. 5. Only a few TFBSs were found to be available in most of AH-genes, including Sp1 binding element.

CONCLUSION

During of ten million years of evolution, the promoter nucleotide sequences of the AGT and AGTR1 gene promoters in 8 primate species (human, gorilla, chimpanzee, Anubis baboon, Tibetan macaque, rhesus macaque, crab-eating *Macaca fascicularis* and common marmoset) show very high (≥85%) similarity. However, only a single TFBS (p53 binding site) motif found to be available in the AGT promoter all of these species. On other side, it was found that the AGTR1 gene promoter from each of the 8 species contains motifs of Sp1, Sp2, Sp3, EGR-1 and MAZ binding sites. So, it can be assumed that the regulatory mechanisms of the transcription of the AGTR1 genes in the studied species, compared to the AGT gene, have been relatively less modified during evolution.

REFERENCES

Achyuthan K.E., Rowland T.C., Birckbichler P.J., Lee K.N., Bishop P.D., Achyuthan A.M. Hierarchies in the binding of human factor XIII, factor XIIIa, and endothelial cell

transglutaminase to human plasma fibrinogen, fibrin, and fibronectin. *Mol. Cell. Biochem*. 1996;162: 43-49. DOI 10.1007/BF00250994

Altschul S.F., Madden T.L., Schaffer A.A., Zhang J., Zhang Z., Miller W., Lipman D.J. Gapped BLAST and PSI-BLAST: a new generation of protein database search programs. *Nucl. Acids Res.* 1997;25: 3389-3402. DOI 10.1093/nar/25.17.3389

Arnason U., Gullberg A. and Janke A. Molecular timing of primate divergences as estimated by two nonprimate calibration points. *J. Mol. Evol.* 1998; 47:718–727. DOI 10.1007/pl00006431

Austin E.D. and Loyd J.E. The genetics of pulmonary arterial hypertension. *Circ Res.* 2014;115(1): 189–202. DOI 10.1161/CIRCRESAHA.115.303404

Batra S.S., Levy-Sakin M., Robinson J., Guillory J., Durinck S., Vilgalys T.P., Pui-Kwok P-Y, Cox L.A., Seshagiri S., Song Y.S. and D Wall J.D. Accurate assembly of the olive baboon (*Papio anubis*) genome using long-read and Hi-C data. *Gigascience*. 2020; 9(12): giaa134. DOI 10.1093/gigascience/giaa134

Bonnardeaux A., Davies E., Jeunemaitre X., Fery I., Charru A., Clauser E., Tiret L., Cambien F., Corvol P., Soubrier F. Angiotensin II type 1 receptor gene polymorphisms in human essential hypertension. *Hypertension.* 1994;24: 63-69. DOI 10.1161/01.hyp.24.1.63

Butler J.E., Kadonaga J.T. The RNA polymerase II core promoter: a key component in the regulation of gene expression. *Genes and Develop*. 2002;16: 2583-2592. DOI 10.1101/gad.1026202

Caulfield M., Lavender P., Farrall M., Munroe P., Lawson M., Turner P., Clark A.J.L. Linkage of the angiotensinogen gene to essential hypertension. *New Eng. J. Med.* 1994; 330: 1629-1633. DOI 10.1056/NEJM199406093302301

Chappell M.C. The Angiotensin-(1-7) Axis: Formation and Metabolism Pathways. Angiotensin-(1-7). *Springer Nature Switzerland*. 2019 Aug 22:1–26. DOI 10.1007/978-3-030-22696-1_1

Chen F.C. and Li W.H. Genomic divergences between humans and other hominoids and the effective population size of the common ancestor of humans and chimpanzees. *Am. J. Hum. Genet.* 2001; 68:444–456. DOI 10.1086/318206

Chinnaraj M., Planer W., Pozi N. Structure of Coagulation Factor II: Molecular Mechanism of Thrombin Generation and Development of Next-Generation Anticoagulants. *Front Med (Lausanne)*. 2018; 5:281; DOI 10.3389/fmed.2018.00281

Dailey L., Roberts S.B., Heintz N. RNA Polymerase II transcription factors H4TF-1 and H4TF-2 require metal to bind specific DNA sequences. *Mol. and Cell. Biology*.1987; 7:4582-4584. DOI 10.1128/mcb.7.12.4582-4584.1987

Doolittle R.F., Feng D.F., Tsang S., Cho G. and Little E. Determining divergence times of the major kingdoms of living organisms with a protein clock. *Science*. 1996; 271:470–477. DOI 10.1126/science.271.5248.470

Easteal S. and Herbert G. Molecular evidence from the nuclear genome for the time frame of human evolution. *J. Mol. Evol.* 1997;44 (Suppl.):121–132. DOI 10.1007/PL00000066

Ebeling M., Küng E., See A., Broger C., Steiner G., Berrera M., Heckel T., Iniguez L., Albert T., Schmucki R., Biller H., Singer T. and Certa U. Genome-based analysis of the nonhuman primate Macaca fascicularis as a model for drug safety assessment. *Genome Res.*2011; 21(10): 1746–1756. DOI 10.1101/gr.123117.111

Eckert D., Buhl S., Weber S., Jäger R., Schorle H. The AP-2 family of transcription factors. *Genome biology*. 2005; *6*(13), 246. DOI 10.1186/gb-2005-6-13-246

Ferreira A.J., Raizada M.K. Could It Be a Novel Target for Neurogenic Hypertension? *Hypertension*. 2008;51:1273–1274. DOI 10.1161/HYPERTENSIONAHA.107.109561

Fish R.J. Fibrinogen gene regulation. *Thromb Haemost.* 2012;108:419-426.,DOI 10.1160/TH12-04-0273.

Garcia-Rivas G., Jerjes-Sánchez C., Rodriguez D., Garcia-Pelaez J., Trevino V . A systematic review of genetic mutations in pulmonary arterial hypertension. *BMC Medical Genetics*. 2017; 18:(82)**.** DOI 10.1186/s12881-017-0440-5

Glazko G.V. and Nei M. Estimation of Divergence Times for Major Lineages of Primate Species. *Mol. Biol. Evol*. 2003;20(3):424–434. DOI 10.1093/molbev/msg050

Hahn S. Structure and mechanism of the RNA polymerase II transcription machinery. *Nat Struct Mol Biol*. 2004;11:394-403. DOI 10.1038/nsmb763.

Homberger A., Linnebank M., Winter C., Willenbring H., Marquardt T., Harms E., Koch H.G. Genomic structure and transcript variants of the human methylenetetrahydrofolate reductase gene. *European J of Human Genetics*. 2000;8:725-729. DOI 10.1038/sj.ejhg.5200522.

Jordan J., Kurschat C., Reuter H. Arterial Hypertension. Diagnosis and Treatment. *Dtsch Arztebl Int.*, 2018;115(33-34):557–568. DOI 10.3238/arztebl.2018.0557

Juven-Gershon T., Hsu J.Y., Theisen J.W., Kadonaga J.T. The RNA polymerase II core promoter—the gateway to transcription. *Curr Opin Cell Biol*. 2008;20:253-259. DOI 10.1016/j.ceb.2008.03.003.

Kraus J.P., Oliveriusová J., Sokolová J., Kraus E., Vlček Č., de Franchis R., Maclean K.N., Bao L., Bukovská G., Patterson D., Pačes V., Ansorge W., Kožich V. The human cystathionine β-synthase (CBS) gene: complete sequence, alternative spslicing, and polymorphisms. *Genomics.* 1998;52: 312-324. DOI 10.1006/geno.1998.5437.

Kunutsor S.K., Powles J.W. The effect of ambient temperature on blood pressure in a rural West African adult population: a cross-sectional study. *Cardiovasc. J. Afr.* 2010;21(1):17-20.

Lifton R.P. Molecular genetics of human blood pressure variation. *Science.* 1996;272:676-680. DOI 10.1126/science.272.5262.6.

Lu H., Cassis L.A., Kooi C.W.V., Daugherty A. Structure and functions of angiotensinogen. *Hypertension Res.* 2016;39:492-500. DOI 10.1038/hr.2016.17.

Lu H., Jiang X., He L., Ji X., Li X., Liu S., Sun Y., Qin X., Xiong X., Philipsen S., Xi B., Zhang M., Yang J., Zhang C., Zhang Y., Zhang W. Endothelial Sp1/Sp3 are essential to the effect of captopril on blood pressure in male mice. *Nature Communications*. 2023;*14*(1):5891. DOI 10.1038/s41467-023-41567-1.

Ly L.L., Yoshida H., Yamaguchi M. Nuclear transcription factor Y and its roles in cellular processes related to human disease. *Am J Cancer Res*. 2013;3(4) 339-346.

Maity G. et al. The MAZ transcription factor is a downstream target of the oncoprotein Cyr61/CCN1 and promotes pancreatic cancer cell invasion via CRAF–ERK signaling. *J Biol. Chem*. 2018;293(12):4334-4349. DOI 10.1074/jbc.RA117.000333

Miyazaki H., Fukamizu A., Hirose S., Hayashi T., Hori H., Ohkubo H., Nakanishi S., Murakami K. Structure of the human renin gene. *Proc Natl Acad Sci (USA).* 1984;81:5999-6003. DOI 10.1073/pnas.81.19.5999.

Pires B.R.B. et al. NF-kappaB: Two Sides of the Same Coin. *Genes.* 2018;9:24. DOI 10.3390/genes9010024.

Puthucheary Z., Skipworth J.R., Rawal J., Loosemore M. The ACE gene and human performance: 12 Years on. *Sports Medicine*. 2011;41:433-48. DOI 10.2165/11588720-000000000-00000

Rogers J., Gibbs R.A. Comparative primate genomics: emerging patterns of genome content and dynamics. *Nat Rev Genet.* 2014;15(5):347–359. DOI 10.1038/nrg3707.

Schier A.C., Taatjes D.J. Structure and mechanism of the RNA polymerase II transcription machinery. *Genes Dev*. 2020;34:465-488. DOI 10.1101/gad.335679.119.

Shahmuradov I.A., Solovyev V.V. Nsite, NsiteH and NsiteM computer tools for studying transcription regulatory elements. *Bioinformatics*. 2015;31:3544-3545. DOI 10.1093/bioinformatics/btv404.

Smale S.T., Kadonaga J.T. The RNA polymerase II core promoter. *Annual Rev of Biochem*. 2003;72:449-479. DOI 10.1146/annurev.biochem.72.121801.161520.

Solovyev V.V., Shahmuradov I.A., Salamov A.A. Identification of promoter regions and regulatory sites. *Computational biology of transcription factor binding*. Humana Press, Totowa, N.J. 2010;674:57-83. DOI 10.1007/978-1-60761-854-6_5.

Stauffer B.L., Dockstader K., Russell G., et al. Transgenic over-expression of YY1 induces pathologic cardiac hypertrophy in a sex-specific manner. *Biochem Biophys Res Commun*. 2015;462(2):131-137. DOI 10.1016/j.bbrc.2015.04.106.

Sullivan et al. Mechanisms of transcriptional regulation by p53. *Cell Death & Differentiation.* 2018;25:133-143.

Vossen C.Y., Callas P.W., Hasstedt S.J., Long G.L., Rosendaal F.R., Bovill E.G. A genetic basis for the interrelation of coagulation factors. *J Thromb Haemost.* 2007;5:1930-1935. DOI 10.1111/j.1538-7836.2007.02678.x.

Wang B. et al. The Role of the Transcription Factor EGR1 in Cancer. *Front. Oncol*. 2021;11:24. DOI 10.3389/fonc.2021.642547.

Wang H. et al. cAMP Response Element-Binding Protein (CREB): A Possible Signaling Molecule Link in the Pathophysiology of Schizophrenia. *Front. Mol. Neurosci*. 2018;11. DOI 10.3389/fnmol.2018.00255.

Weiss L.A., Veenstra-VanderWeele J., Newman D.L., Kim S-J., Dytch H., McPeek M.S., Cheng S., Ober C., Edwin H Cook Jr., Abney M. Genome-wide association study identifies *ITGB3* as a QTL for whole blood serotonin. *European J of Human Genetics.* 2004;12:949-954. DOI 10.1038/sj.ejhg.5201239

Woychik N.A., Hampsey M. The RNA polymerase II machinery: structure illuminates function. *Cell*. 2002;108:453-463. DOI 10.1016/S0092-8674(02)00646-3.

Wu C-H., Mohammadmoradi S., Chen J.Z., Sawada H., Daugherty A. and Lu H.S. Renin-Angiotensin System and cardiovascular functions. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2018;38:108–116. DOI 10.1161/ATVBAHA.118.31128.

Zinan O.K.H., Keseroğlu K., Özbudak E.M. Regulatory mechanisms ensuring coordinated expression of functionally related genes. *Trends Genet*. 2022;38(1):73-81. DOI 10.1016/j.tig.2021.07.008

İNSAN VƏ DİGƏR BƏZİ PRİMATLARDA AGT VƏ AGTR1 GENLƏRİNİN PROMOTOR NAHİYYƏLƏRİNİN NÖVLƏRARASI KONSERVATİVLİYİ

Zümrüd Abaszadə[1], Aysel Əliyeva[2], Lalə Məmmədova[2], İlham Şahmuradov[2,3*]

[1] Azərbaycan Tibb Universiteti

,[2] Azərbaycan Respublikası Elm və Təhsil Nazirliyi Biofizika İnstitut

[3] Azərbaycan Respublikası Elm və Təhsil Nazirliyi Genetik Ehtiyatlar İnstitutu

İnsan, qorilla (*Gorilla gorilla*), şimpanze (*Pan troglodytes*), anubis meymunu (*Papio anubis*), Tibet makak meymunu (*Macaca thibetana*), Rezus makak meymunu (*Macaca mulatta*), krab yeyən meymun (*Macaca fascicularis*) və adi marmot meymununun (*Callithrix jacchus*) AGT və AGTR1 genlərinin promototrlarının növlərarası konservativliyi xüsusiyyətlərinin kompütetr analizi aparılmışdır. Hər iki genin promotor rayonlarında blok şəklində müəyyən yenidənqurmalar baş versə də, bütövlükdə nukleotid ardıcıllığı səviyyəsində onlar arassında yüksək dərəcədə (≥85%) oxşarlıq saxlanmışdır. AGT və AGTR1 genlərində TFBS-larının növlərarası konservativlik dərəcəsini qiymətləndirmək üçün həmin genlərin hamsının yaxud böyük hissəsinin promotorunda mövcud olan TFBS motivlərinin axtarışı həyata keçirilmişdir. Aşkar olunmuşdur ki, yalnı p53 ilə birləşmə saytının motive 8 növün hər birinin AGT geninin promotor nahiyyəsində vardır. Digər tərəfdən, məlum olmuşdur ki, AGTR1 geni bu baxımdan daha konservativdir. Belə ki, Sp1, Sp2, Sp3, EGR-1 və MAZ transkripsiya faktorları ilə birləşmə saytlarının motivləri 8 növün hər birinin AGTR1 geninin promotorunda mövcuddur. Bu nəticələrə əsasən güman olunur ki, AGT geni ilə müqayisədə, AGTR1 geninin transkripsiyasının tənzimlənmə mexanizmləri on milyonlarla il sürən təkamülün gedişində nisbətən az dəyişikliyə məruz qalmışdır. Bu işdə həmçinin AH ilə əlaqəli genlərin funksional əlaqəli qrupunun razılaşdırılmış ekspressiyasında ınəlaqələndirilmiş ifadəsində TF/TFBS-lərin rolu araşdırılmışdır. Bu məqsədlə AH ilə əlaqəli 12 genin TFBS tərkibinin müqayisəli analizi həyata keçirilmişdir. AH genlərinin əksəriyyətində,Sp1 ilə birləşmə saytı daxil olmaqla,yalnız bir neçə potensial TFBS-nin mövcudluğu aşkar edilmişdir.

Açar sözlər: *arterial hipertenziya, AGT geni, AGTR1 geni, promotor, transkripsiya faktorları, promotor analizi.*

МЕЖВИДОВАЯ КОНСЕРВАЦИЯ ПРОМОТОРОВ ГЕНОВ AGT И AGTR1 У ЧЕЛОВЕКА И НЕКОТОРЫХ ДРУГИХ ПРИМАТОВ

Зюмруд Абасзаде[1], Айсель Алиева[2], Лала Мамедова[2] , Ильхам Шахмурадов [2,3]*
[1]Азербайджанский медицинский университет
[2]Институт биофизики Министерства науки и образования Азербайджанской Республики
[3]Институт генетических ресурсов Министерства науки и образования Азербайджанской Республики

Проведен компьютерный анализ особенностей межвидовой консервации промоторов генов AGT и AGTR1 у 8 видов приматов: человека (*Homo sapiens*), гориллы (*Gorilla gorilla*), шимпанзе (*Pan troglodytes*), павиана-анубиса (*Papio anubis*), тибетской макаки (*Macaca thibetana*), макака-резус (*Macaca mulatta*), макака-крабоед (*Macaca fascicularis)* и мармосета обыкновенная (*Callithrix jacchus*). Было обнаружено, что хотя в процессе эволюции в промоторных областях как генов AGT, так и AGTR1 этих видов произошли некоторые блоковые перестройки, нуклеотидные последовательности промоторов демонстрируют очень высокое (85%) сходство. Для оценки уровня межвидовой консервативности некоторых сайтов связывания транскрипционных факторов (ССТФ)в промоторах AGT и AGTR1 был проведен поиск мотивов ССТФ, имеющихся в промоторах всех или большинства этих генов этих видов. Было обнаружено, что в промоторе AGT всех этих видов имеется только один мотив ССТФ (сайт связывания p53). Однако в случае промотора гена AGTR1 он оказался более консервативным. Так, промотор гена AGTR1 каждого из 8 видов содержит мотивы ССТФ Sp1, Sp2, Sp3, EGR-1 и MAZ. По этим результатам можно предположить, что регуляторные механизмы транскрипции генов AGTR1 у изученных видов, по сравнению с геном AGT, за десять миллионов лет эволюции подверглись сравнительно меньшей модификации. В этой работе мы также исследовали роль ТФ/ССТФ в скоординированной экспрессии функционально родственной группы генов, связанных с АГ. С этой целью мы провели сравнение ССТФ-содержания 12 генов, связанных с АГ. Было обнаружено, что лишь несколько ССТФ-мотивы в большинстве АН-генов, включая сайт связывания Sp1.

Ключевые слова:*артериальная гипертензия, ген AGT, ген AGTR1, промотор, факторы транскрипции, промоторный анализ.*

Çapa təqdim etmişdir: Zeynal Əkpərov, AMEA-nın müxbir üzvü, a.e.d, professor
Redaksiyaya daxil olma tarixi: 26.07.2024
Təkrar işlənməyə göndərilmə tarixi: 15.08.2024
Çapa qəbul edilmə tarixi: 20.09.2024