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Original article

Unraveling the Evolutionary Trajectory, and Functional Significance of ALOX5AP: A Proteomic Investigation

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ABSTRACT

Background and aims*. Coronary artery disease (CAD) is a condition that disrupts blood flow to the heart and includes heart attacks, remaining a leading cause of death. The enzyme LTA4H is involved in the inflammatory pathways associated with CAD. ALOX5AP encodes a protein necessary for leukotriene production, which contributes to atherosclerosis progression.* ***Methods.*** *This study aims to analyze ALOX5AP protein diversity, evolution, and selection pressures to understand its biological function. Information was gathered on phylogenetic relationships, and the BLAST tool was used to identify similar proteins and genes. Multiple sequence alignment and phylogenetic tree construction were performed.* ***Results.*** *The highest distribution density of ALOX5AP was observed in Homo sapiens, followed by isoforms of other organisms. Evaluation of selection pressures indicated purifying selection in most codons, with a few showing neutral or positive selection.* ***Conclusion.*** *The study found that Tupaia chinensis is likely the earliest known form of ALOX5AP, while Homo sapiens represents the most recent sequences, suggesting a rapid evolution in primates and other higher organisms, and that positive selection of ALOX5AP isoforms in Homo sapiens may contribute to the higher prevalence of ALOX5AP proteins in human CAD.*

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INTRODUCTION

Coronary artery disease (CAD) is a condition characterized by a problem with the blood supply to the heart, which includes heart attacks and is a leading cause of death in many countries. There are well-established risk factors for CAD, such as diabetes, high cholesterol, high blood pressure, smoking, a high-fat diet, and obesity [1-2]**.** Recently, there has been a growing interest in understanding the genetic basis of CAD. This interest has been fueled by the use of powerful tools like genome-wide scans, which have identified numerous genes associated with CAD. Most of these genes are involved in the inflammatory pathways related to the disease. Some examples of these genes include lymphotoxin-α, galectin-2, proteasome subunit α-type 6, and leukotriene A4 hydrolase. Another gene called ALOX5AP, which encodes the 5-lipoxygenase-activating protein, has also been found to be associated with CAD and heart attacks [3-6]. ALOX5AP is a protein that belongs to the MAPEG superfamily and is located on chromosome 13. It consists of 5 exons and is made up of 161 amino acids. Its main role is in the production of leukotriene A4, which is involved in the development of atherosclerosis. Studies have shown that certain variations in the ALOX5AP gene, known as haplotypes, are associated

with an increased risk of heart attacks and strokes [7-9]**.** However, research on ALOX5AP in different populations has sometimes yielded conflicting results. While studies in Central Europe have found significant associations between certain gene variations and an increased risk, studies in North America have not consistently shown a significant association with stroke or heart attacks [10-12]**.** In the pathway for leukotriene synthesis, ALOX5AP, which is encoded by the ALOX5AP gene, plays a role in enhancing the reaction that produces leukotriene A4. Although ALOX5AP itself does not have enzymatic activity, it enhances the activity of the enzyme 5-lipoxygenase. The products of this pathway, including leukotrienes, have been implicated in various diseases, such as asthma, allergies, and atherosclerosis [13-17]**.** It is worth noting that there is currently a lack of genetic epidemiological data on the population of North Africa. Additionally, previous studies have not specifically focused on the role of ALOX5AP in the development of atherosclerosis, instead primarily examining its role in heart attacks. Therefore, to investigate the potential role of ALOX5AP and its haplotypes as risk factors for CAD and heart attacks, we conducted an analysis using computational tools to explore the evolutionary relationship and structure of ALOX5AP.

METHODS

We conducted a comprehensive study on the protein architecture of each member of the ALOX5AP family in Homo sapiens by utilizing Boolean queries on the NCBI's Gene database. In order to obtain accurate results, we employed strict parameters for our homolog searches, ensuring that only genuine positive results were included. We utilized the Genbank and genpept databases to retrieve gene sequences, coding sequences (CDS), and protein sequences in Fasta format [18-19,34]**.**

To eliminate any artificial constructs and sequences that did not align well with our queries, we utilized the NCBI BLAST tools blastn and blastp to search against a NonRedundant Database Our main objective was to determine the evolutionary changes in individual genomes and examine the distribution of the ALOX5AP family. For tree creation and clustering, we utilized the Topali software [20]. Phylogenetic trees at the protein level were generated using neighbor-joining with a bootstrapping iteration value of 100. This allowed us to explore the evolutionary history of the ALOX5AP family [21].

To estimate the 3D structure of the selected isoform of each member of the Human ALOX5AP family, we employed the ab-initio methodology of the I-TASSER server [22]. The structural models were evaluated using the PROCHECK tool to assess their stereochemical quality [23]. We further analyzed the top models for each unique isoform. In order to determine the presence of positive or negative selection at specific amino acid sites in the full-length ALOX5AP sequences, we used the SELECTON server to calculate the substitution rate ratios of nonsynonymous (Ka) versus synonymous (Ks) mutations. A Ka/Ks ratio above 1 indicates positive selection, while a ratio below 1 indicates purifying selection. This analysis allowed us to gain insights into the evolutionary processes shaping the ALOX5AP family [24].

RESULTS AND DISCUSSION

The objective of this study was to investigate the diversity of the ALOX5AP protein in various species within the animal kingdom and explore its evolutionary origins. Initially, a multiple sequence alignment of ALOX5AP was conducted using cluster X. The presence or absence of functional residues at or near the aligned positions, as well as the percentage of identity, were recorded in Table 1.

Table 1. Homologs and Percentage Bio-distribution density of ALOX5AP proteins

No	Accession number	Organisms	Identity	Paralogs	Homologs	Biodistribution (%)
1	NP_001620	Homo sapiens 1	%100.00	3	7	7.07
2	NP_001191335	Homo sapiens 3	%100.00			
3	CAA36441	Homo sapiens 4	%100.00			
4	2Q7M_A	Homo sapiens 2	%99.38	2		
5	1603359A	Homo sapiens 6	%99.38			
6	6VGC_A	Homo sapiens 5	%98.76	1		
7	2Q7R_A	Homo sapiens 7	%98.12	1		
8	XP_031321696	Camelus dromedarius 1	%93.58	1	3	3.03
9	KAB1267621	Camelus dromedarius 2	%93.79	1		
10	XP_010975428	Camelus dromedarius 3	%93.70	1		
11	XP_003919756	Saimiri boliviensis boliviensis 1	%98.14	1	2	2.02
12	XP_003919757	Saimiri boliviensis boliviensis 2	%98.14	1		
13	NP_001253418 XP_001100572	Macaca mulatta 1	%98.10	1	2	2.02

14	P30354	Macaca mulatta	%98.04	1		
15	XP_002914800	Ailuropoda melanoleuca 1	%94.00	1	2	2.02
16	XP_019650246	Ailuropoda melanoleuca 2	%94.41	1		
17	EQB78819	Camelus ferus 1	%93.17	2	2	2.02
18	XP_006189655	Camelus ferus 2	%93.17			
19	XP_030674272	Nomascus leucogenys	%99.38	1	1	1.01
20	XP_004054383	Gorilla gorilla gorilla	%100.00	1	1	1.01
21	PNI60458	Pan troglodytes	%100.00	1	1	1.01
22	XP_032006426	Hylobates moloch	%99.38	1	1	1.01
23	XP_003913776	Papio anubis	%98.14	1	1	1.01
24	XP_023064539	Piliocolobus tephrosceles	%99.38	1	1	1.01
25	XP_024086641	Pongo abelii	%99.38	1	1	1.01
26	XP_004604602	Sorex araneus	%98.14	1	1	1.01
27	XP_007958252	Chlorocebus sabaeus	%97.52	1	1	1.01
28	XP_032150307	Sapajus apella	%97.52	1	1	1.01
29	XP_002806930	Callithrix jacchus	%97.52	1	1	1.01
30	XP_011802311	Colobus angolensis palliatus	%98.76	1	1	1.01
31	XP_029792743	Suricata suricatta	%96.89	1	1	1.01
32	XP_010365382	Rhinopithecus roxellana	%98.14	1	1	1.01
33	XP_011920035	Cercocebus atys	%98.14	1	1	1.01
34	XP_035575818	Canis lupus dingo	%96.27	1	1	1.01
35	XP_011823226	Mandrillus leucophaeus	%98.14	1	1	1.01
36	XP_025220054	Theropithecus gelada	%98.14	1	1	1.01
37	XP_017721450	Rhinopithecus bieti	%98.14	1	1	1.01
38	XP_017373888	Cebus imitator	%96.89	1	1	1.01
39	XP_006927255	Felis catus	%95.65	1	1	1.01
40	XP_033091928	Trachypithecus francoisi	%98.14	1	1	1.01
41	VFV46043	Lynx pardinus	%95.65	1	1	1.01
42	XP_014687434	Equus asinus	%95.65	1	1	1.01
43	XP_025852529	Vulpes vulpes	%95.65	1	1	1.01
44	KAF0873161	Crocuta crocuta	%95.65	1	1	1.01
45	XP_004854838	Heterocephalus glaber	%95.65	1	1	1.01
46	XP_008690420	Ursus maritimus	%95.03	1	1	1.01
47	XP_006158488	Tupaia chinensis	%95.65	1	1	1.01
48	XP_032735893	Lontra canadensis	%94.41	1	1	1.01
49	NP_001157437 XP_001493446	Equus caballus	%95.03	1	1	1.01
50	XP_024436613	Desmodus rotundus	%95.65	1	1	1.01
51	XP_012602007	Microcebus murinus	%95.03	1	1	1.01
52	XP_006832010	Chrysochloris asiatica	%93.79	1	1	1.01
53	XP_037384593	Talpa occidentalis	%94.41	1	1	1.01
54	XP_004774865	Mustela putorius furo	%94.41	1	1	1.01
55	XP_004435358	Ceratotherium simum simum	%94.41	1	1	1.01
56	XP_036985474	Artibeus jamaicensis	%95.03	1	1	1.01
57	XP_036893012	Sturnira hondurensis	%95.03	1	1	1.01
58	XP_004680241	Condylura cristata	%94.41	1	1	1.01
59	XP_025730880	Callorhinus ursinus	%93.79	1	1	1.01
60	XP_007522464	Erinaceus europaeus	%93.79	1	1	1.01
61	XP_028388592	Phyllostomus discolor	%95.03	1	1	1.01
62	XP_004406694	Odobenus rosmarus divergens	%95.03	1	1	1.01
63	XP_021533944	Neomonachus schauinslandi	%93.79	1	1	1.01
64	XP_036773206	Manis pentadactyla	%93.79	1	1	1.01
65	XP_020030777	Castor canadensis	%93.79	1	1	1.01
66	XP_008157681	Eptesicus fuscus	%94.41	1	1	1.01
67	XP_032259140	Phoca vitulina	%93.79	1	1	1.01
68	XP_022376396	Enhydra lutris kenyoni	%93.17	1	1	1.01
69	XP_005317127	Ictidomys tridecemlineatus	%93.79	1	1	1.01
70	XP_008055031	Carlito syrichta	%94.41	1	1	1.01
71	XP_012497584	Propithecus coquereli	%94.41	1	1	1.01
72	XP_003477308	Cavia porcellus	%93.79	1	1	1.01
73	XP_010622177	Fukomys damarensis	%93.79	1	1	1.01
74	XP_002720652	Oryctolagus cuniculus	%95.03	1	1	1.01
75	XP_004660044	Jaculus jaculus	%93.17	1	1	1.01
76	XP_006763783	Myotis davidii	%94.41	1	1	1.01
77	XP_003797654	Otolemur garnettii	%93.79	1	1	1.01
78	XP_034858808	Mirounga leonina	%95.03	1	1	1.01
79	XP_008823262	Nannospalax galili	%93.79	1	1	1.01
80	XP_035955554	Halichoerus grypus	%93.17	1	1	1.01

81	XP_010949833	Camelus bactrianus	%93.17	1	1	1.01
82	XP_006904861	Pteropus alecto	%93.17	1	1	1.01
83	VTJ67356	Marmota monax	%93.79	1	1	1.01
84	XP_006085525	Myotis lucifugus	%93.17	1	1	1.01
85	XP_026244172	Urocitellus parryii	%93.17	1	1	1.01
86	XP_012882733	Dipodomys ordii	%93.17	1	1	1.01
87	XP_016069050	Miniopterus natalensis	%93.17	1	1	1.01
88	XP_016007360	Rousettus aegyptiacus	%92.55	1	1	1.01
89	XP_036108626	Molossus molossus	%93.79	1	1	1.01
90	XP_036602188	Trichosurus vulpecula	%92.55	1	1	1.01
91	XP_010592296	Loxodonta africana	%92.55	1	1	1.01
92	XP_006979671	Peromyscus maniculatus bairdii	%91.93	1	1	1.01
93	XP_005387798	Chinchilla lanigera	%92.55	1	1	1.01
94	XP_005877322	Myotis brandtii	%92.55	1	1	1.01
95	XP_011358495	Pteropus vampyrus	%92.55	1	1	1.01
96	XP_028733902	Peromyscus leucopus	%91.93	1	1	1.01
97	XP_020852888	Phascolarctos cinereus	%91.93	1	1	1.01
98	XP_020740048	Odocoileus virginianus texanus	%91.93	1	1	1.01
99	KAF4025666 WMHW01000000	Cervus hanglu yarkandensis	%92.55	1	1	1.01
Total				99	99	100%

Additionally, the candidates were subjected to phylogenetic analysis, biodiversity assessment, and selection pressure analysis. Although an initial screen using BLASTP revealed similar sequences with local matches, further investigation was required to determine if these candidates possessed the necessary features of a COX enzyme [25]. The phylogenetic analysis of the ALOX5AP protein at the protein level clearly demonstrated that the protein family could be grouped into two distinct clusters comprising fourteen different subgroups. In Figure 1 and Table 1, it can be observed that the ALOX5AP protein is distributed in the 14th cluster.

The 2nd cluster, represented by Tupaia chinensis, appears to be the original sequence from which other organisms in this group evolved. The 3rd cluster includes Otolemur garnettii, which is closely related to the 2nd cluster (Tupaia chinensis), while Ceratotherium simum simum diverged in the 1st cluster. Within the 2nd cluster, the 3rd subgroup consists of Crocuta crocuta, Chrysochloris asiatica, and Desmodus rotundus. The 4th cluster includes Suricata suricatta, Equus caballus, Equus asinus, Carlito syrichta, and Callithrix jacchus in the 1st subgroup, while Lynx pardinus, Erinaceus europaeus, Sturnira hondurensis, and Manis pentadactyla are found in the 2nd subgroup. The 5th cluster is associated with animals in the 2nd cluster, as indicated in Figure 1 and Table 1.

The 13th cluster, found in the 1st subgroup, consists of Homo sapiens isoforms 4, 6, and 1, which diverged parallelly with Pan troglodytes and Gorilla gorilla gorilla. The query sequence is located in the 14th cluster, which diverged parallelly with Homo sapiens isoforms 2, 3, and 5, as shown in figure 1 and table 1. Many authors have previously observed a similar trend of phylogenetic divergence among members of the ALOX5AP protein reported that two highly homologous proteins from different species or two highly homologous ALOX5AP proteins within the same species may not necessarily perform the same function [26-33]. However, this view contradicts a later report suggesting that members grouped into subclusters of the same cluster may share a similar function or exhibit less functional divergence compared to those grouped into distant clusters [31].

In all ALOX5AP proteins, the Homo sapiens-specific sequences are evenly distributed across the newest clusters. This distribution pattern was also observed in other members of the Order Primates, including Pan troglodytes. The protein-level biodistribution of ALOX5AP in selected animal members is presented in table 1. The highest percentage biodistribution density was observed in Homo sapiens (7.07%), followed by Camelus dromedarius isoforms 1, 2, and 3 (3.03%), Saimiri boliviensis boliviensis isoforms 1 and 2, Macaca mulatta isoforms 1 and 2, Ailuropoda melanoleuca isoforms 1 and 2, and Camelus ferus isoforms 1 and 2 (2.02%) respectively, while the remaining animals exhibited a biodistribution of 1.01%. It is noteworthy that Homo sapiens itself constitutes the highest percentage of the overall ALOX5AP protein biodistribution. Furthermore, despite playing a crucial role in various life processes, the highest distribution density (7.07%) was observed in Homo sapiens (Table 1, Figure 1). This anomaly was further examined through an analysis of the selection pressures influencing the complexity of the ALOX5AP protein. SELECTON server was employed to evaluate the various selection pressures on all the sites of the randomly selected type of ALOX5AP. A site-specific selection pressure analysis was performed using the SELECTON server Table 2 on all selected protein structures of the longest ALOX5AP forms were modeled by the I-TASSER server using the ab-initio methodology. The study of selection pressures revealed that the majority of the codons ALOX5AP were under purifying selection with

78.26%, 16.14% showed a neutral selection and 5.59% showed in positive selection when taking into account the distribution of the computed Ka/Ks ratio (ω). In this particular situation, Brosnan and Iacobuzio-Donahue (2012) recently highlighted the importance of understanding the occurrences that experience both advantageous and disadvantageous selection during the development of disease [32]. They suggested that this understanding would not only significantly enhance our knowledge of disease evolution, but also aid in identifying potential targets for therapeutic intervention. However, a significant number of research articles lack specific data on the isoforms of disease -associated genes in different organisms [33]. This lack of data makes it challenging to analyze the selection process that occurs at various sites of these proteins.

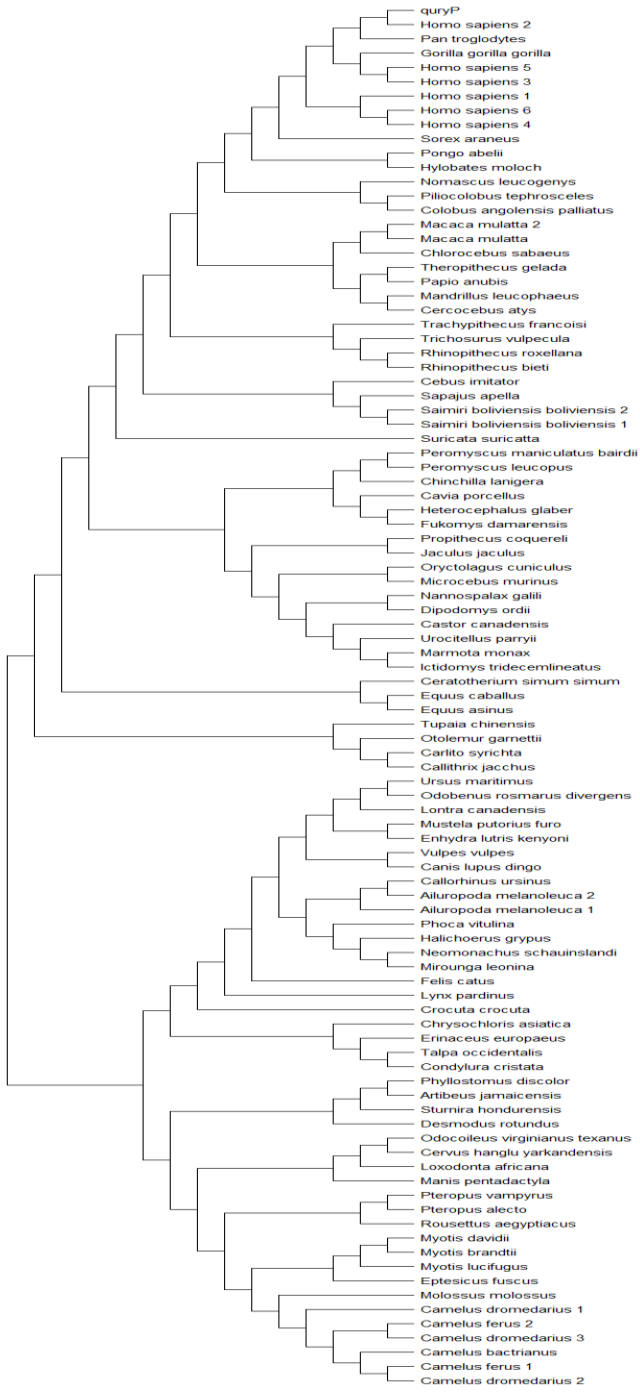

Figure 1. Phylogenetic analysis of ALOX5AP at protein level

Table 2. Analysis of Biological significance of ALOX5AP protein

Sequence length	Organisms	Representation of Ka/Ks (ω) sites			Percentage ω site representation		
		ω <1	**ω =1**	**ω >1**	**ω <1 (%)**	**ω =1 (%)**	ω >1 (%)
161	Homo Sapiens	126	26	9	78.26	16.14	**5.59**

CONCLUSION

Based on the findings of our research, we have come to the conclusion that Tupaia chinensis is likely the earliest known form of ALOX5AP among the various sequences. It is interesting to note that this particular species possesses the initial two clusters, which later developed into two new subfamilies of ALOX5AP. On the other hand, Homo sapiens, representing the most recent ALOX5AP sequences, suggests a rapid expansion in the evolution of primates and other closely related higher organisms. Interestingly, within the Homo sapiens sequence, we observed that 5.59% of ALOX5AP isoforms exhibited positive selection, which could potentially explain the higher prevalence of ALOX5AP proteins in human CAD, despite their comparatively lower distribution when compared to other organisms.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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كشف المسار التطوري والأهمية الوظيفية لـ :ALOX5AP دراسة بروتينية

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المستخلص

الخلفية والأهداف. مرض الشريان التاجي (CAD) هو حالة تعطل تدفق الدم إلى القلب وتشمل النوبات القلبية، وتظل السبب الرئيسي للوفاة. ويشارك إنزيم LTA4H في المسارات الالتهابية المرتبطة بمرض .CAD يشفر ALOX5AP البروتين الضروري لإنتاج الليكوترين، مما يساهم في تطور تصلب الشرايين. **طرق الدراسة**. تهدف هذه الدراسة إلى تحليل تنوع بروتين ALOX5AP وتطوره وضغوط الاختيار لفهم وظيفته البيولوجية. تم جمع المعلومات عن العلاقات التطورية، وتم استخدام أداة بلاست لتحديد البروتينات والجينات المماثلة. تم إجراء محاذاة تسلسل متعددة وبناء شجرة النشوء والتطور. **النتائج**. لوحظت أعلى كثافة توزيع لـ ALOX5AP في الإنسان العاقل، تليها الأشكال الإسوية للكائنات الحية الأخرى. أشار تقييم ضغوط الاختيار إلى انتقاء تنقية في معظم الكودونات، مع ظهور عدد قليل منها اختيارًا محايدًا أو إيجابيًا. **الاستنتاج**. وجدت الدراسة أن Tupaia chinensis هو على الأرجح أقدم شكل معروف لـALOX5AP ، في حين يمثل الإنسان العاقل أحدث التسلسلات، مما يشير إلى تطور سريع في الرئيسيات والكائنات العليا الأخرى، وأن الاختيار الإيجابي لأشكال ALOX5AP الإسوية في الإنسان العاقل قد يساهم في ارتفاع معدل انتشار بروتينات ALOX5AP في CAD البشري.

الكلمات الدالةALOX5AP .، التطور، الشجرة التطورية، ضغط الاختيار.