Evolutionary patterns of interleukin-6 (Il-6) and its impact on human health

https://doi.org/10.56238/sevened2024.007-030

Arthur Felipe Ferreira de Freitas[1], Nara Suzy Aguiar de Freitas[2], Maria Helena Queiroz de Araújo Mariano[3], Eliézer Rushansky[4] and Maria de Mascena Diniz Maia[5]

ABSTRACT

Interleukin-6 (IL-6) is a multifunctional cytokine with properties pleiotropic derived from a polymorphic gene. The IL6 gene is located on the short arm of human chromosome 7 and containing four exons and four introns. The cytokine IL-6 is an important signaling agent between cells as the inflammatory reaction develops. Since cytokines are essential for life, studies show that the overproduction of IL-6 is often involved in various pathologies. It is well established that the frequency of different alleles of the cytokine genes varies between different populations of different species of mammals. Thus, this work aims to identify the relationship of synteny in relation to the preservation of order and the interaction between group of genes in the same chromosomal region based on the orthologs of the human IL6 gene in other five species of eutherian mammals and to investigate the selective signature of the IL6 gene in order to find conserved patterns in the genomes of mammals analyzed to observe their evolutionary history. We analyzed 40 genes adjacent to the IL6 gene in the genomes of Homo sapiens, Pan troglodytes, Gorilla gorilla, Pongo abelii, Camelus ferus and Equus asinus. The genetic sequences were obtained using the BLAST tool and aligned using the MEGA 11 program. We reviewed the literature looking for associations between the IL6 gene and its neighbors reported in previous studies. Finally, we analyzed the non-synonymous to synonymous substitution rates (dN/dS) between genomes in order to determine the selective signature of the IL6 gene. Among the 40 neighboring genes analyzed, only 11 were found to be in synteny, being present in all genomes. The conservation of these genes in different mammals suggests that IL6 and genes close to it may have evolved from a common ancestor and have been kept grouped together due to selective pressures during evolution. Furthermore, we found the NUP42 gene, which due to its moleculares properties, can influence the expression of the IL6 gene. The dN/dS ratio revealed a negative signature in the IL6 gene, which indicates that natural selection acts to maintain its conserved sequence, rejecting possible amino acid changes. Therefore, we conclude that our findings indicate that the IL6 gene remains conserved in the human genome during evolution. It is also noted that this gene may be influenced by its neighbors. With emphasis on the presence of the NUP42 gene, located

[1] Graduating in Biological Sciences
Institution: Federal Rural University of Pernambuco
Address: Rua Dom Manuel de Medeiros, Dois Irmãos, Recife – PE, Brazil
E-mail: arthur.ffreitas@ufrpe.br
[2] PhD in Genetics from the Federal University of Pernambuco
Institution: Federal Rural University of Pernambuco
Address: Rua Dom Manuel de Medeiros, Dois Irmãos, Recife – PE, Brazil
E-mail: nara.safreitas@ufrpe.br
[3] Dr. in Biological Sciences from the Federal University of Pernambuco
Institution: University of Pernambuco
Address: Rua Arnóbio Marques, Santo Amaro, Recife – PE, Brazil
E-mail: irpe.diretoria@gmail.com
[4] Post-graduation in Internal Medicine from the University of Pernambuco
Institution: University of Pernambuco
Address: Rua Arnóbio Marques, Santo Amaro, Recife – PE, Brazil
E-mail: eliezer.rushansky@upe.pe.gov.br
[5] Dr. in Biological Sciences from the Federal University of Pernambuco
Institution: Federal Rural University of Pernambuco
Address: Rua Dom Manuel de Medeiros, Dois Irmãos, Recife – PE, Brazil
E-mail: maria.dmaia@ufrpe.br

close to IL6, which can act to regulate the expression of this cytokine in the body. Therefore, we suggest that future investigations include the evaluation of protein-DNA and protein-protein interactions in analyzes with the IL6 gene.

Keywords: Selective signature, Synteny, Evolutionary medicine, dN/dS, Evolutionary history.

INTRODUCTION

The body's defense mechanisms depend both on conserved hereditary factors and on variations that pass through the sieve of natural selection and genetic drift (Konopinski, Fijarczyk & Biedrzycka, 2022). When combined with different environments, pathogens exert a strong selective pressure on their hosts. The fight between the hosts' immune system and pathogens, in a coevolutionary context, allows the fixation of efficient alleles within the population, due to positive selection (Kosiol *et al*., 2008; Nielsen *et al*., 2005). Conserved genomic patterns can be biomarkers of physiological processes necessary for the defense system of various organisms. Thus, analyzing genes related to the immune system are promising options to understand the genomic basis of the evolutionary processes of numerous human pathologies.

Evolutionary medicine brings with it approaches to population genetics and investigates health on past, current, and future microevolutionary changes in human structure, function, and pathologies (Rühli & Henneberg, 2013). In the past, medical genetics and evolutionary biology have been misused in eugenic theories (Brüne, 2007). Therefore, understanding the diversity of humans and other living beings, as well as the changes that have occurred in historical times, and still occur, helps us to combat structural prejudices and explain medical conditions. This alert reveals to clinicians how their current practices can influence future intergenerational care, given that nucleotide sequences show few non-synonymous variations when compared between different species.

One way to broaden the horizons in the search for patterns when studying the evolution of a gene is the analysis of the degree of synteny, which refers to the collinearity of specific sequences of certain genes in distinct species, that is, a block of genes conserved in an orderly manner within two sets of chromosomes compared to each other (Sinha, 2007). This method helps in the perception of the patterns conserved between species, being one of the most reliable methods to establish the ontology between genomic regions in different species (Amores, 1998). The collinear orders of a group of genes can present interactions that are decisive to exert their physicochemical attributions in an organism, and are then essentially preserved in heterogeneous groups of individuals belonging to distinct species, that is, the high degree of conservation of synteny can be strongly linked to important functional relationships between neighboring genes (Amores, 1998). The analysis of shared synteny patterns can be used as an important tool to infer phylogenetic relationships between various species.

All genomes are subject to the pressure of natural selection, which can be detected by their molecular signature, ω = dN/dS, i.e., the ratio of non-synonymous to synonymous substitutions in a given nucleotide sequence (Nielsen, 2005; Gillespie, 1991). Natural selection is one of the fundamental principles that drive the evolution of organisms. This theory is based on the premise that

heritable traits that increase the fitness of individuals are more likely to become more prevalent in populations over time, while traits that reduce fitness tend to be eliminated (Fisher, 1930). Natural selection can act in a directional way (positive or negative). Positive selection is responsible for driving an increase in the frequency of adaptive mutations in the population, while negative selection, also known as purifying, acts in the opposite direction, reducing the frequency or eliminating deleterious mutations from populations (Hartl & Clark, 1997). It can also act as a balancer, being responsible for providing the maintenance of genetic diversity in populations.

In this study, we chose to analyze the IL6 gene, located on chromosome 7 in humans (region 7p21-p15), which is responsible for the synthesis of interleukin-6 (IL-6), a pleiotropic cytokine that plays an important role in immunomodulation (Dinarello, 2007; Freitas *et al.*, 2022). IL-6 triggers the inflammatory process and contributes significantly to host defense in response to infectious agents (Rivers-Auty *et al*., 2018; McCrae *et al.*, 2023). On the other hand, the dysregulated production of this cytokine can contribute to deleterious pathological effects in several autoimmune and inflammatory diseases and in several types of cancer (Freitas *et al.,* 2022). The synthesis of interleukin-6 is regulated by a complex network of cell signaling pathways and transcription factors. The gene expression of interleukin-6 can be influenced by factors such as the activation of inflammatory signaling pathways, cellular stress, and hormones (Akira & Takeda, 2004). However, there is still a large gap in knowledge about the regulatory mechanisms and other factors that can influence the synthesis of interleukin-6.

Overall, the evolutionary history and origins of interleukins are not yet fully understood by science (Kubick *et al*., 2021). Some studies indicate that cytokines were an evolutionary innovation and arose in jawed vertebrates (Rivers-Auty *et al.*, 2018). Therefore, studies that seek to understand the evolution of ILs become essential for the understanding of several pathologies associated with cytokines (Kubick *et al.*, 2021).

Thus, this study sought to identify the synteny relationship related to the preservation of order between genes grouped in the same chromosomal region based on the orthologs of human IL6 in five different species of eutherian mammals. We also explored the selective signature of the IL6 gene in order to find conserved patterns in this set of genomes and highlight the importance of research in evolutionary medicine. By analyzing the synteny and pressure of natural selection, we aim to probe the evolutionary history of interleukins-6 and its relevance to diverse medical conditions.

METHODOLOGY

SEQUENCE ALIGNMENT

Five species of eutherian mammals with genomic contexts available in the databases were selected: *Pan troglodytes, Gorilla gorilla, Pongo abelii, Camelus ferus and Equus asinus*. The

nucleotide sequences homologous to the human IL6 gene in the other species were acquired using the BLAST (Basic Alignment Search Tool) of the NCBI (National Center for Biotechnology Information). The Mega 11 computational software was used to perform the alignment and editing of the nucleotides, allowing the analysis of the substitutions present in the comparisons between the various species of mammals.

SELECTION OF GENES IN SYNTENY

Genomic data were acquired using the NCBI for localization and analysis of the influence of 40 genes adjacent to the IL6 gene. A detailed observation of the 20 genes located before and after the position of IL6 in chromosome 1 of Equus *asinus and* in chromosome 7 of the other species was performed. Exclusively the genes present in human chromosome 7 and in the other species were selected, disregarding other genes in synteny in the different species, except in *Homo sapiens.Databases* of scientific articles (PubMed, SciELO and Google Scholar) were used to understand the functions and effects of each gene in the organism. The analysis sought to associate the functions of each neighboring gene with the IL6 gene, aiming to identify possible relationships that highlight the importance of conserving this gene block in the organisms analyzed.

ANALYSIS OF THE RATE OF NON-SYNONYMOUS SUBSTITUTIONS BY SYNONYMS (DN/DS)

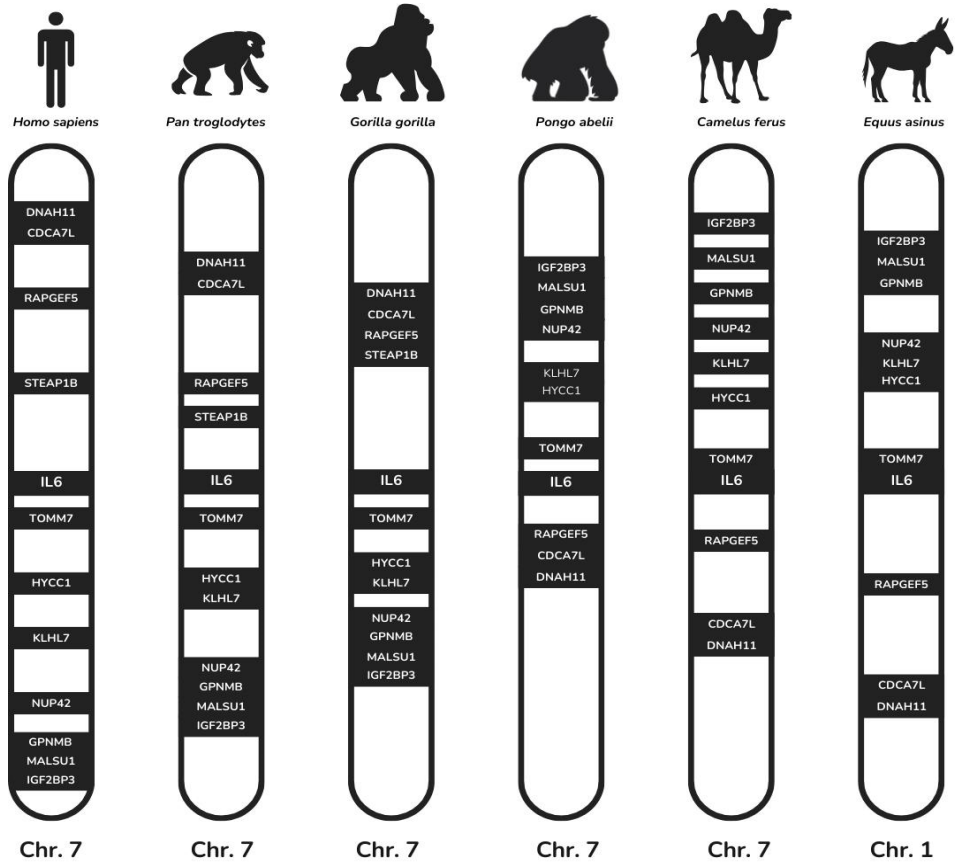
The dN/dS ratio was calculated using the MEGA 11 software, using the Kumar method, as outlined by Nei & Kumar (2000). The objective of this study was to evaluate the relationship between non-synonymous (dN) and synonymous (dS) rates of change in an evolutionary context, seeking to understand the processes of selection and adaptation in orthologous sequences to the IL6 gene in *Homo sapiens, Pan troglodytes, Pongo abelii, Camelus ferus* and *Equus asinus.*

RESULTS AND DISCUSSION

By analyzing the data obtained, it was identified the presence of 11 genes in synteny with IL6 in the species *Homo sapiens, Pan troglodytes, Gorilla gorilla, Pongo abelii, Camelus ferus and Equus asinus*. Figure 1 shows the representation of the chromosomes of each species and the position of the gene cluster present in all the organisms evaluated, consisting of the following genes: DNAH11, CDCA7L, RAPGEF5, TOMM7, HYCC1, KLHL7, NUP42, GPNMB, MALSU1, IGF2BP3, except for the STEAP1B gene, which, in the scale of genes observed, was located only in *H. sapiens*, *P. troglodytes* and *G. gorilla*. The distances in base pairs between the highlighted genes are important for understanding the speciation effects that contributed to the evolutionary divergence in this group of organisms.

In the species *H. sapiens*, *P. troglodytes* and *G. gorilla,* the presence of a group composed of four genes (DNAH11, CDCA7L, RAPGEF5 and STEAP1B) located before the IL6 gene can be observed. While the second gene block composed of TOMM7, HYCC1, KLHL7, NUP42, GPNMB, MALSU1, IGF2BP3, are clustered in a position after the IL6 gene. This chromosomal structure observed in the aforementioned species is not repeated in the other species analyzed. *P. abelii, C. ferus and E. asinus* present these two gene blocks in an inverted way, indicating that there was a chromosomal inversion in these organisms (Figure 1). The conservation of genes in synteny between humans and other mammals suggests that the IL6 gene and other genes close to it may have evolved from a common ancestor and have been kept grouped together due to the same selective pressures during evolution.

Figure 1. A set of genes neighboring IL6 that are in synteny among the six eutherian mammalian species studied.



Source: Prepared by the author, 2024.

Table 1. Correlation of the pathophysiological effects of IL6-close genes with diseases in which the cytokine IL-6 can also have a negative influence.

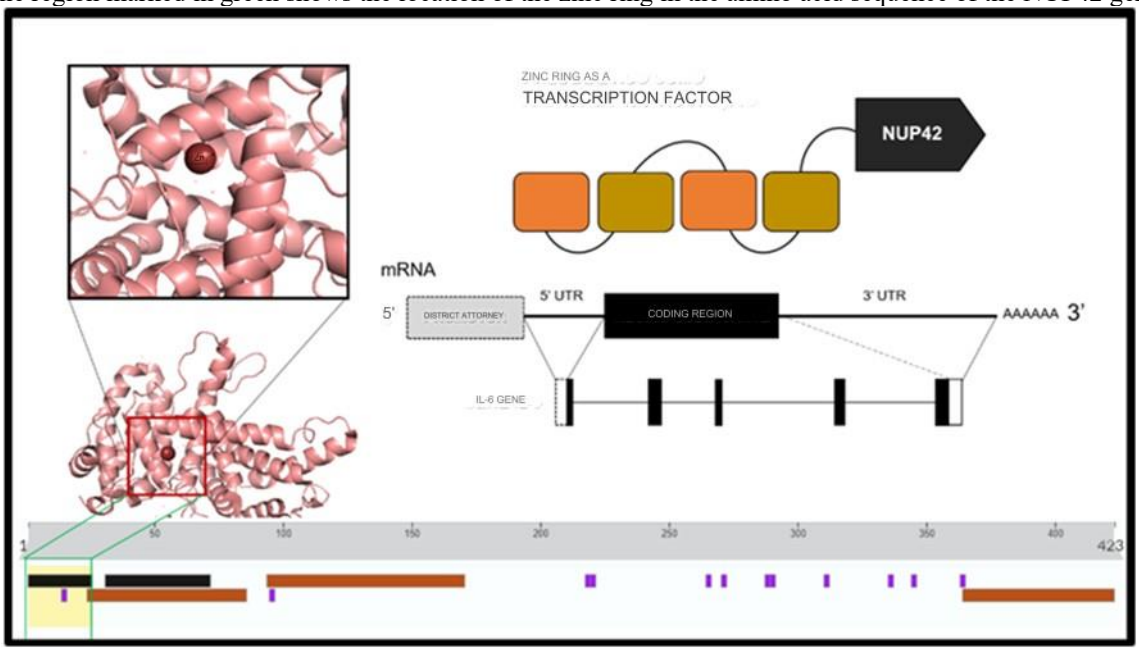
Gene	Associated Issues	Reference	IL-6	Reference
DNAH11	Congenital heart disease in humans	Xia *et al.* (2021)	Significant increases in the inflammatory process in patients with congenital heart disease.	Tavares *et al.* (2022)
CDCA7L	Human glioma	Shen *et al.* (2019)	IL-6 is associated with tumorigenesis and predicts poor prognosis in patients with glioma.	Liu *et al.* (2021)
RAPGEF5	Aplastic anemia	Officers & Mandal (2019)	Serum IL-6 levels are associated with increased severity in aplastic anemia	Bhargawa et al. (2022)
STEAP1B	Prostate Cancer	Gomes *et al.* (2014)	Elevated levels of interleukin-6 are commonly reported in patients with prostate cancer	Natani (2021)
TOMM7	Deficiency of gene product expression may be linked to an impairment in cerebral angiogenesis	Li *et al.* (2022)	Responsible for causing imbalance in angiogenesis	Breuer *et al.* (2021)
HYCC1	Progressive neurological impairment and myelin deficiency in the central and peripheral nervous system.	Traverso *et al.* (2013)	High levels of IL-6 are linked to the process of neurodegeneration of the central nervous system	Cabral *et al.* (2011)
KLHL7	Retinite pigmentosa	Oh (2019)	Serum levels of IL-6 trigger an inflammatory process that may be the main cause of corneal changes associated with retinitis pigmentosa.	Take small *meat.* (2019)
NUP42	No problems associated with this gene have been found	-	-	-
GPNMB	Neuroinflammation	Show *et al.* (2021)	The cytokine IL-6 may be linked to neuroinflammation	Dhapola *et al.* (2021)
MALSU1	No problems associated with this gene have been found	-	-	-
IGF2BP3	Oncogenic Effect on Human Bladder Cancer Progression	Huang *et al.* (2020)	Interleukin 6 may be related to the progression of human bladder cancer.	Goulet *et al.* (2019)

Source: Survey data.

Most of these genes have high medical importance associated with immunopathologies, neurodegenerative diseases, and multiple types of cancer (Table 1). The data compiled on these genes indicate that it is possible to relate them to IL6 in different pathogen-phenotypes. Among the genes, the NUP42 gene stands out, which, although there are no relations with IL6 yet described in the literature, it is possible that this is a molecular regulator capable of modulating IL-6 expression, due to the presence of a conserved zinc ring domain C3H1 in its structure. This domain may confer on the protein the ability to interact with the untranslated 3' region of IL6 gene mRNAs and allow modulation of interleukin-6 expression (Stenzel *et al*., 2018) (Figure 2). NUP42 regulates the gene quantity expressed, attributing functional differences in immunological characteristics in the population. This means that the phenotypic expression of IL6 may depend on the influence of the epigenetic mechanism exerted on the host immune system.

The identification of genes such as NUP42, which can modulate IL-6 expression, is a significant breakthrough in the field of medical research, as this cytokine is an important molecule for the inflammatory response, being involved in a variety of pathological conditions. In functional terms, the presence of regulatory genes in close proximity to the IL-6 gene can facilitate the coordination of gene expression, allowing them to be activated or deactivated in a coordinated manner in response to specific signals from the environment (King *et al.*, 2007). Understanding the regulatory mechanisms of IL-6 expression is critical for the development of new immunotherapies and effective treatments for several diseases. In addition, the identification of genes that can modulate IL-6 expression may provide new *insights* for the development of highly specific and effective therapeutic drugs, which can be used in clinical practice. Moreover, the fact that this gene is observed in other species suggests a possible evolutionary conservation of this regulatory element in conjunction with IL6. Several factors can influence the conservation of the gene cluster, such as natural selection itself, which can act to maintain the coordinated expression of genes involved in specific cellular processes, ensuring their structure and function conserved over evolutionary time.

Figure 2. Schematic representation of the binding of the conserved zinc ring domain present in the gene product of the NUP42 gene in the coding region of the mRNA of the human IL6 gene with its promoter. The presence of this domain can modulate human IL-6 expression, influencing gene activity and affecting its expression at the mRNA and protein level. The region marked in green shows the location of the zinc ring in the amino acid sequence of the NUP42 gene.



Source: Prepared by the author, 2024.

The IL6 gene arose through genetic duplications followed by base alterations, favoring an increase in non-synonymous substitutions compared to synonymous ones, this means that the evolution of this gene was marked by a positive signature, as pointed out by Kubick *et al*. (2021). Table 2 shows the dN/dS ratio values obtained using Kumar's method, which uses the Kimura 2-

parameter model to compare non-synonymous (dN) and synonymous (dS) substitution rates between orthologous sequences of the gene (Nei and Kumar, 2000). H . *sapiens/P. troglodytes* (0.00432), *H. sapiens/G. gorilla* (0.0132), *H. sapiens/P. abelii* (0), *H. sapiens/C. ferus* (0.251), *H. sapiens/E. asinus* (0.191), *P. troglodytes/G. gorilla* (0.00884), P. *troglodytes/P. abelii* (0.00432), *P. troglodytes/C. ferus* (0.244), *P. troglodytes/E. asinus* (0.185), *G. gorilla/P. abelii* (0.132), *G. gorilla/C. ferus* (0.249), *G. gorilla/E. asinus* (0), *P. abelii/C. ferus* (0.251), *P. abelii/E. asinus* (0.191) and *C. ferus/E. asinus* (0.181).

It is assumed that the evolutionary process of immune-related genes, such as interleukins, is initially driven by positive selection (McTaggart *et al*., 2012; Schlenke & Begun, 2003). However, our results suggest that the IL6 gene is under negative selection pressure in all species, considering that our results showed values lower than one (>1) (Table 2). Thus, it can be seen that the process of diversification of interleukins is quite old and the interleukin-6 gene remains conserved among the different species analyzed, which emphasizes the evolutionary importance of the gene. However, the reconstruction of ancestor sequences is not always accurate enough to infer molecular phylogenetic relationships between species (Schierholt *et al*., 2008). Therefore, it is necessary to use other tests in order to confirm our results and ensure greater precision about the evolutionary history of the IL6 gene.

In non-pathological conditions, cytokines of the IL-6 family are related to the development and functions of the central nervous system in response to a variety of stimuli, such as infections, inflammation, and stress, with effects on various cells of the body (Taga and Fukuda, 2005). Thus, the highly preserved functionality among species indicates a strong tendency for the conservation of function during evolution and, thus, its adaptive value tends to be preserved, which makes it a good indicator of evolutionary health. Although the IL6 gene is conserved in the human genome, several genetic variants have been identified and identified as causing or potentiating many physiological and pathological processes, especially in autoimmune diseases (Hirano, 2010; Freitas *et al*., 2022; Castanhola *et al*., 2022).

Table 2. Results of the rate of non-synonymous substitutions for synonyms (dN/dS).

	H. sapiens	*P. troglodytes*	*G. gorilla*	*P. abelii*	*C. ferus*	*E. asinus*
H. sapiens		0.00432	0.0132	0	0.251	0.191
P. troglodytes			0.00884	0.00432	0.244	0.185
G. gorilla				0.132	0.249	0.000
P. abelii					0.251	0.191
C. ferus						0.181
E. asinus						

Source: Survey data.

FINAL THOUGHTS

Our findings indicate that the IL6 gene remains conserved in the human genome, as evidenced by the negative selection pressure exerted on the gene and by the degree of the gene block in synteny among the organisms analyzed. In addition, it is perceived that the human IL6 gene has a significant influence on neighboring genes, and can even act together. The effort of researchers to analyze and understand the effects of polymorphisms in the IL6 gene during the regulatory processes of inflammation in the development of diseases is notorious, however, we suggest that future investigations include the evaluation of the interactomes of this gene, with emphasis on the NUP42 gene, considered a molecular switch with high relevance to be explored.

REFERENCES

1. Adhikari, S., & Mandal, P. (2019). Integrated analysis of global gene and microRNA expression profiling associated with aplastic anaemia. Life Sciences, 1(228), 47-52.

2. Akira, S., & Takeda, K. (2004). Toll-like receptor signalling. Nature Reviews Immunology, 7, 499-511.

3. Amores, A., Force, A., Yan, Y., et al. (1998). Zebrafish hox clusters and vertebrate genome evolution. Science, 282(5394), 1711–1714.

4. Bhargawa, S. K., Singh, A., Yadav, G., Kushwaha, R., Verma, S. P., Tripathi, A. K., & Singh, U. S. (2022). Aplastic anemia severity and IL-6 and IL-8 blood levels. Discoveries, 10(4).

5. Breuer, S., et al. (2021). Brain-restricted inhibition of IL-6 trans-signaling mildly affects metabolic consequences of maternal obesity in male offspring. Nutrients, 13(11), 3735.

6. Brüne, M. (2007). On human self-domestication, psychiatry, and eugenics. Philosophy, Ethics, and Humanities in Medicine, 2, 21.

7. Cabral, B. L. S., Lima, L. C. N., Jesus, J. D., et al. (2011). Avaliação dos níveis séricos de interleucina 6 e das alterações no mini-exame do estado mental na doença de Alzheimer. 63ª Reunião Anual da SBPC.

8. Castanhola, M. E., Tibúrcio, B. C. S., Ramos, L. C., Silva, N. S. B., et al. (2022). O papel da imunogenética no desenvolvimento de lúpus eritematoso sistêmico/The role of immunogenetics in the development of systemic lupus erythematosus. Brazilian Journal of Development, 8(4), 26564–26573.

9. Dhapola, R., Hota, S. S., Sarma, P., Bhattacharyya, A., Medhi, B., & Reddy, D. H. (2021). Recent advances in molecular pathways and therapeutic implications targeting neuroinflammation for Alzheimer's disease. Inflammopharmacology, 6, 1669-1681.

10. Dinarello, C. A. (2007). Historical insights into cytokines. European Journal of Immunology.

11. Fisher, R. A. (1930). The genetical theory of natural selection, 154.

12. Freitas, A. F. F., Freitas, N. S. A., Montes, M. A., & Maia, M. M. D. (2022). In silico analysis of the impact of non-synonymous single nucleotide polymorphisms (nsSNPs) in the human il-6 gene related to autoimmune diseases. International Journal of Sciences, 3(1), 01-05.

13. Gillespie, J. H. (1991). The causes of molecular evolution. Oxford University Press.

14. Gomes, I. M., Santos, C. R., & Maia, C. J. (2014). Expression of STEAP1 and STEAP1B in prostate cell lines, and the putative regulation of steap1 by post-transcriptional and post-translational mechanisms. Genes & Cancer, 5(3–4), 142–151.

15. Goulet, C. R., Champagne, A., Bernard, G., Vandal, D., Chabaud, S., Pouliot, F., & Bolduc, S. (2019). Cancer-associated fibroblasts induce epithelial-mesenchymal transition of bladder cancer cells through paracrine IL-6 signalling. BMC Cancer, 19(1), 137.

16. Hartl, D., & Clark, A. G. (1997). Principles of population genetics. Sinauer Associates, 3rd edition.

17. Hirano, T. (2010). Interleucina 6 em doenças autoimunes e inflamatórias: um livro de memórias pessoais. Proceedings of the Japan Academy, 86, 717-30.

18. Huang, W., Li, Y., Zhang, C., et al. (2020). IGF2BP3 facilitates cell proliferation and tumorigenesis via modulation of JAK/STAT signaling pathway in human bladder cancer. Journal of Cellular and Molecular Medicine, 24(23), 13949–13960.

19. King, D. C., Taylor, J., Zhang, Y., Cheng, Y., Lawson, H. A., & Martin, J. Encode groups for transcriptional regulation and multispecies sequence analysis; Chiaromonte, F., Miller, W., & Hardison, R. C. (2007). Finding cis-regulatory elements using comparative genomics: some lessons from ENCODE data. Genome Research, 7(6), 775-86.

20. Konopiński, M. K., Fijarczyk, A. M., & Biedrzycka, A. (2023). Complex patterns shape immune genes diversity during invasion of common raccoon in Europe – Selection in action despite genetic drift. Evolutionary Applications, 16(1), 134-151.

21. Kosiol, C., Vinar, T., Fonseca, R. R., Hubisz, M. J., Bustamante, C. D., Nielsen, R., & Siepel, A. (2008). Patterns of positive selection in six mammalian genomes. PLoS Genetics, 4(8).

22. Kubick, N., et al. (2021). Interleukins and interleukin receptors evolutionary history and origin in relation to CD4+ T cell evolution. Genes, 12(6), 813.

23. Küçük, B., Yıldırım, Y., & Özsaygılı, C. (2019). Anterior chamber characteristics assessed by rotating Scheimpflug imaging in patients with retinitis pigmentosa. Arquivos Brasileiros de Oftalmologia, 82, 507-510.

24. Li, Z., et al. (2022). Identification of potential blood biomarkers for early diagnosis of schizophrenia through RNA sequencing analysis. Journal of Psychiatric Research, 147, 39-49.

25. Liu, S., et al. (2021). Regulatory T cells promote glioma cell stemness through TGF-β–NF-κB–IL6–STAT3 signaling. Cancer Immunology, Immunotherapy, 1-16.

26. McCrae, L. E., Ting, W., & Howlader, M. M. R. (2023). Advancing electrochemical biosensors for interleukin-6 detection. Biosensors and Bioelectronics: X, 13, 100288.

27. McTaggart, S. J., Obbard, D. J., Conlon, C., & Little, T. J. (2012). Immune genes undergo more adaptive evolution than non-immune system genes in Daphnia pulex. BMC Evolutionary Biology, 12(1), 63.

28. Natani, S., et al. (2021). AMPK/SIRT1 signaling through p38MAPK mediates Interleukin-6 induced neuroendocrine differentiation of LNCaP prostate cancer cells. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1868(10), 119085.

29. Nei, M., & Kumar, S. (2000). Molecular evolution and phylogenetics. Oxford University Press.

30. Nielsen, R. (2005). Molecular signatures of natural selection. Annual Review of Genetics, 39, 197–218.

31. Nielsen, R., et al. (2005). A scan for positively selected genes in the genomes of humans and chimpanzees. PLoS Biology, 3(6).

32. Oh, J. K., Carvalho, J. R. L., Sun, Y. J., et al. (2019). Novel mutations in the 3-box motif of the back domain of KLHL7 associated with nonsyndromic autosomal dominant retinitis pigmentosa. Orphanet Journal of Rare Diseases, 14(1), 295.

33. Rivers-Auty, J., et al. (2018). Redefining the ancestral origins of the interleukin-1 superfamily. Nature Communications, 9(1), 1156.

34. Rühli, F. J., & Henneberg, M. (2012). New perspectives on evolutionary medicine: the relevance of microevolution for human health and disease. BMC Medicine, 11, 115.

35. Saade, M., Souza, G. A., Scavone, C., et al. (2021). The role of GPNMB in inflammation. Frontiers in Immunology, 12, 674739.

36. Schierholt, A. S., et al. (2008). Análise filogenética do gene da miogenina. Arquivo Brasileiro de Medicina Veterinária e Zootecnia, 60, 156-162.

37. Schlenke, T. A., & Begun, D. J. (2003). Natural selection drives Drosophila immune system evolution. Genetics, 164(4), 1471–1480.

38. Shen, F., Li, X., Ma, J., et al. (2019). Cell division cycle associated 7 like predicts unfavorable prognosis and promotes invasion in glioma. Pathology - Research and Practice, 215(1), 50–56.

39. Sinha, A. U., & Meller, J. (2007). Cinteny: flexible analysis and visualization of synteny and genome rearrangements in multiple organisms. BMC Bioinformatics, 8(1), 82.

40. Stenzel, P., Nagorsen, K., Bernd, J., et al. (2018). ZNF580 – a brake on interleukin-6. Journal of Inflammation, 15(1), 20.

41. Taga, T., & Fukuda, S. (2005). Role of IL-6 in the neural stem cell differentiation. Clinical Reviews in Allergy & Immunology, 28, 249-256.

42. Tavares, I. P. C., et al. (2022). Interferencia de polimorfismos no gene IL-6 na contagem global e relativa de leucócitos em recém-nascidos com cardiopatia congênita. Hematology, Transfusion and Cell Therapy, 44, 77-78.

43. Traverso, M., Assereto, S., Gazzerro, E., et al. (2013). Novel FAM126A mutations in hypomyelination and congenital cataract disease. Biochemical and Biophysical Research Communications, 439(3), 369–372.

44. Xia, H., Huang, X., Deng, S., et al. (2021). DNAH11 compound heterozygous variants cause heterotaxy and congenital heart disease. PLoS One, 16(6), e0252786.