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Keywords: abiraterone; prostate; amazonian; indigenous; cancer

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Genomic Investigation for Potential Therapeutic Use of Abiraterone in the Amazonian Indigenous Population

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Abstract: Prostate cancer, according to the World Health Organization (WHO), ranks as the fourth most prevalent type in the population, even though it is highly frequent when detected early and promptly treated, resulting in a low mortality rate. However, in some cases, despite adherence to proper clinical protocols, there is a progression to castration-resistant prostate cancer (CRPC). In these cases, as outlined in clinical guidelines such as those developed by the National Comprehensive Cancer Network (NCCN), one approach involves the utilization of the pharmaceutical agent abiraterone to implement androgen deprivation therapy (ADT), aimed at suppressing the production of hormones directly implicated in disease progression. Another noteworthy aspect is the limited literature on clinical protocols and their efficacy concerning the Amazonian indigenous population, which often exhibits unique genomic profiles, with descriptions of variants not yet documented in the literature. Building upon these considerations, this study aims to survey the variants identified in genes associated with the abiraterone signaling pathway, their frequencies in the Amazonian indigenous population, and the correlation of these frequencies with those observed in other global populations. The objective is to contribute to the refinement of clinical practices in the treatment of prostate cancer within this population.

Keywords: abiraterone; prostate; amazonian; indigenous; cancer

1. Introduction

The worldwide incidence of prostate cancer, as reported by the World Health Organization, reached 1.2 million individuals, securing the fourth position in terms of case numbers. The mortality rate stands at approximately 40%, with studies suggesting that poorer prognoses are more closely associated with the European population [21].

The clinical approach to addressing this type of cancer depends on the stage of the disease. In more advanced stages, according to the National Comprehensive Cancer Network (NCCN), one of the approaches involves implementing androgen deprivation therapy (ADT). In this context, one of the drugs used is abiraterone [17], which acts as a selective inhibitor of the enzyme CYP17.

Even after the implementation of ADT protocols, some patients develop a more aggressive form of the disease called castration-resistant prostate cancer (CRPC), in which there is high expression of steroid hormones that ultimately promote disease recurrence and shorter survival time.

After studies, it has been observed that individuals who progress to CRPC exhibit variants in the HSD3B1 gene. This gene is already described as a biomarker for the occurrence of CRPC and has clinical indications on the PharmGKBD portal [1,3] and regulatory bodies such as the FDA.

Focusing on the ADT protocol, the signaling pathway of the drug abiraterone was examined, revealing five related genes: SLCO2B1, SULT2A1, CYP3A4, HSD3B1, HSD3B2, and UGT1A4. As can be seen, the HSD3B1 gene, associated with CRPC occurrence, is present in this pathway.

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The aim of this article is to assess variants found in genes of the abiraterone signaling pathway in the indigenous population of the Amazon, including the variant of the HSD3B1 gene related as a biomarker for CRPC, and compare the frequencies found with those already verified in other global populations. The analysis also seeks to validate the unique character of the indigenous population studied, reinforcing the need for a specific approach to precision medicine and hormone therapy to benefit this population.

2. Materials and Methods

2.1 Population Analyzed in the Study

The analyzed indigenous population comprises indigenous peoples from the Amazon, totaling 64 individuals who are part of 12 indigenous tribes from the northern region of Brazil: Asurini from the Xingu and Tocantins localities, Arara, Araweté, Awa-Guajá, Juruna, Kayapó, Xikrin, Karipuna, Munduruku, Phurere, Wajãpi, and Zo'é. These tribes were collectively grouped as the Indigenous (INDG) population for statistical analyses. Genetic data were obtained with the consent of all individuals and their leaders, who completed and signed a specific form for this purpose. The entire study and information gathering were approved by the national ethics committee (CONEP) and the ethics committee of the Center for Tropical Medicine at the Federal University of Para (CAE: 20654313.6.0000.5172).

The frequencies of indigenous peoples were compared with those of other continental populations: Europe (EUR), Africa (AFR), East Asia (EAS), South Asia (SAS), and the Americas (AMR). These datasets were sourced from the 1000 Genomes Database, version 3 (available at: http://www.1000genomes.org; accessed on Feb 2, 2024). The study included 503 individuals from Europe, 661 from Africa, 504 from East Asia, 489 from South Asia, and 347 from the Americas.

2.2. DNA Extraction and Exome Analysis

DNA extraction was conducted following the Phenol-Chloroform method [19] with modifications. The extracted product's quantity was measured using a Nanodrop-8000 spectrophotometer (Thermo Fisher Scientific Inc., Wilmington, DE, USA), and the prospective analysis of the extracted material's quality was performed through 2% agarose gel electrophoresis.

2.3. Gene Selection

Gene selection was performed by consulting the PharmGKB database (https://www.pharmgkb.org/pathway/PA166310681; accessed on March 20, 2024). The five selected genes (SLCO2B1, SULT2A1, CYP3A4, HSD3B1, HSD3B2, and UGT1A4) are related to the signaling pathway of the drug abiraterone, which is the focus of this study in prostate cancer treatment.

2.4. Statistical and Bioinformatic Analysis

The allele frequency of the studied population was obtained by gene counting and compared with other major populations already investigated (EUR, AMR, EAS, SAS, and AFR). Fisher's exact test was used to assess the statistical significance in frequency differentiation between populations. The population variability of polymorphisms was observed through Wright's fixation index (FST). A p-value ≤ 0.05 was considered significant. The entire investigation was conducted using RStudio v.3.5.1. Bioinformatic analyses followed the procedures described by Cohen-Paes et al., 2022 [22].

2.5. Inclusion Criteria

The inclusion criteria for SNPs were as follows: (i) a minimum of 10 coverage reads (fastx_tools v.0.13 http://hannonlab.cshl.edu/fastx_toolkit/, accessed in January 2024); (ii) variant impact: modifier, moderate, or high (SNPeff classification (https://pcingola.github.io/SnpEff/, accessed in March 2024); and (iii) allelic and genomic frequency in worldwide populations (http://www.1000genomes.org, accessed in March 2024).

3. Results

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One of the treatment approaches for prostate cancer involves androgen deprivation therapy (ADT), aiming to reduce testosterone production [1]. Among the drugs used to implement this protocol are those containing the substance abiraterone [2]. However, in some cases, despite the application of this protocol, some patients develop castration-resistant prostate cancer (CRPC). Upon investigating possible mechanisms underlying this resistance, a mutation in the HSD3B1 gene was discovered, which has been identified as a potential biomarker for poor prognosis when ADT is implemented [4].

Taking the gene identified as the biomarker HSD3B1 and other genes involved in the drug signaling pathway, including SLCO2B1, SULT2A1, CYP3A4, HSD3B1, HSD3B2, and UGT1A4, as a starting point, we investigated the described variants, their distribution across the global population. Our objective was to identify which of these variants are present in the indigenous population of the Amazon, with the aim of mapping whether variants associated with the HSD3B1 gene and other genes in the pathway are also prevalent in this demographic.

Based on the genes outlined in the signaling pathway illustrated in Figure 01, 46 variants were identified, among which a mutation was found that had only been described in the indigenous population, initially indicated as having low impact. As shown in Figure 02, there is a predominance of variants with modifier impact, comprising 64.3% of the total variants, followed by 21.4% of variants with moderate impact and 14.3% of variants with low impact. Upon analyzing the genes separately, it can be observed that the SULT2A1 gene has the highest percentage of variants with moderate impact, accounting for 80% of all variants described for this gene, followed by the UGT1A4 gene (75.86%), CYP3A4 (66.67%), SLCO2B1 (60%), and HSD3B1 (22.22%).

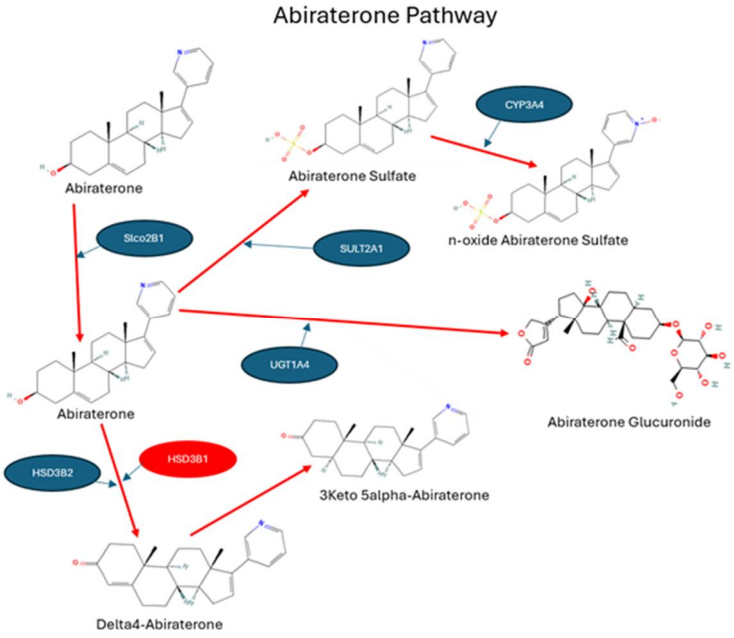

Figure 1. Genes present in the signaling pathway of the drug abiraterone.

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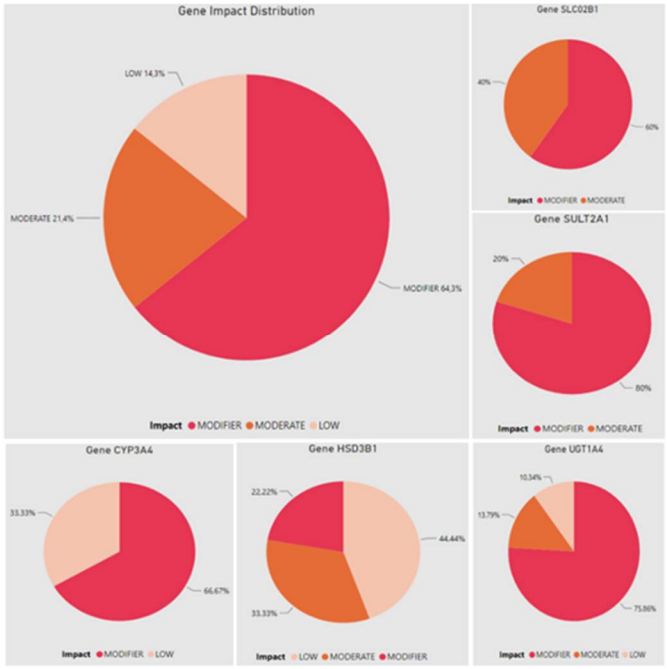

Figure 2. Distribution of mutations across the genes present in the signaling pathway of the studied drug.

Out of a total of 56 variants, 48 were selected with modifier and moderate impacts, and one variant not described in the databases used, initially classified as having low impact. In terms of variant allocation by gene, there are three for the CYP3A4 gene, five for the HSD3B1 gene, ten for the SLCO2B1 gene, five for the SULT2A1 gene, and twenty-six for the UGT1A4 gene. The new variant found in the indigenous population, associated with rfseq NM_017460.5, SNV type, in the CDS region, was identified in the CYP3A4 gene.

Table 1 presents the characteristics of these variants, including their reference number, chromosomal region, nucleotide exchange, predicted impact by the SNPeff software, and allelic frequency related to the indigenous group (IND) and the five continental populations present in the 1000 Genomes Program (AFR, AMR, EAS, EUR, and SAS).

Regarding variant types, thirty-six variants are predicted to have a modifier impact, and twelve have a moderate impact. In terms of location, thirty-three were found in intronic regions, thirteen in the CDS region, two in the 5'UTR region, and one in the 3'UTR region. It was observed that variants predicted to have a modifier impact are all located in the 3'UTR, 5'UTR, and intronic regions, while all variants with a moderate impact are located in the CDS region.

Focusing on the HSD3B1 gene, which is identified as a biomarker for increased CPRC recurrence, only one variant was found in the indigenous population.

Data for all identified variants will be available in a supplementary table.

Table 1. - Variants found and their distribution in the global and indigenous populations.

Gene	SNP ID	Region	Impact	IND	AFR	AMR	EAS	EUR	SAS
CYP3A4	.	cds	low	0,0179	0	0	0	0	0
CYP3A4	rs12721620	Intronic	Modifier	0,0161	0,2671	0,0118	0	0,0006	0,008
CYP3A4	rs2687116	Intronic	Modifier	0	0,3782	0,9165	0,9982	0,9624	0,9629
HSD3B1	rs1047303	Cds	Moderate	0	0,8897	0,8599	0,9376	0,6797	0,8118
HSD3B1	rs6201	Cds	Moderate	0	0,33	0,0794	0,0412	0,003	0,0557
HSD3B1	rs6205	Cds	Moderate	0,0391	0,39	0,0844	0,0428	0,0034	0,0561
HSD3B1	rs6671149	Intronic	Modifier	0	0,151	0,046	0,055	0,003	0,049
HSD3B1	rs6673653	Intronic	Modifier	0	0,1	0,04	0,054	0,002	0,05
SLCO2B1	rs12422149	Cds	Moderate	0,6667	0,0953	0,4573	0,3336	0,1094	0,2231

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SLCO2B1	rs149765874	Cds	Moderate	0	0	0,0001	0	0,0002	0,001
SLCO2B1	rs2306168	Cds	Moderate	0,1349	0,3431	0,0972	0,2308	0,0266	0,0619
SLCO2B1	rs60113013	Cds	Moderate	0	0,0038	0,0618	0,1107	0,0211	0,0379
SLCO2B1	rs12287059	Intronic	Modifier	0,0135	0,1543	0,0074	0	0,001	0,0002
SLCO2B1	rs1944612	5utr	Modifier	1	0,9999	0,9994	0,8861	0,9992	0,9961
SLCO2B1	rs2851069	5utr	Modifier	0,0676	0,144	0,372	0,268	0,622	0,555
SLCO2B1	rs7125268	Intronic	Modifier	0,1429	0,4186	0,5222	0,3276	0,2235	0,3283
SLCO2B1	rs74885054	Intronic	Modifier	0,1087	0,089	0,386	0,311	0,116	0,302
SLCO2B1	rs995893327	Intronic	Modifier	0	0	0,0002	0	0	0
SULT2A1	rs11569679	Cds	Moderate	0	0,1248	0,0048	0	0,0003	0,0007
SULT2A1	rs11569678	3utr	Modifier	0,0161	0,049	0,049	0	0	0
SULT2A1	rs2547238	Intronic	Modifier	0,0833	0,026	0,367	0,506	0,284	0,355
SULT2A1	rs62531056	Intronic	Modifier	0,0405	0,0007	0,0627	0,0003	0	0,0007
SULT2A1	rs767511533	Intronic	Modifier	0	0	0,0001	0	0	0
UGT1A4	rs2011425	cds	Moderate	0	0,0986	0,1275	0,2065	0,0907	0,1996
UGT1A4	rs3892221	cds	Moderate	0	0,0429	0,0011	0,005	0,0011	0,0006
UGT1A4	rs45540231	cds	Moderate	0	0,0641	0,0032		0,0001	0,0002
UGT1A4	rs6755571	cds	Moderate	0	0,0162	0,0215	0,0001	0,0553	0,0102
UGT1A4	rs10929301	Intronic	Modifier	0	0,7048	0,4579	0,3323	0,4511	0,6108
UGT1A4	rs12466997	Intronic	Modifier	0,0811	0,288	0,107	0,225	0,069	0,201
UGT1A4	rs12471326	Intronic	Modifier	0,1111	0,0489	0,1074	0,0038	0,0296	0,0174
UGT1A4	rs199892897	Intronic	Modifier	0	0,086	0,004	0	0	0
UGT1A4	rs2011219	Intronic	Modifier	0	0,0519	0,1106	0,1979	0,0598	0,1759
UGT1A4	rs2302538	Intronic	Modifier	0	0,425	0,097	0,052	0,128	0,157
UGT1A4	rs2361501	Intronic	Modifier	0	0,8134	0,4585	0,2834	0,4469	0,6085
UGT1A4	rs28898618	Intronic	Modifier	0,0208	0,0172	0,0005	0	0	0,0001
UGT1A4	rs28900402	Intronic	Modifier	0	0,104	0,006	0	0	0,066
UGT1A4	rs34547608	Intronic	Modifier	0	0,099	0,007	0,001	0	0
UGT1A4	rs34622615	Intronic	Modifier	0	0,0519	0,0165	0,0017	0,0307	0,0194
UGT1A4	rs34650714	Intronic	Modifier	0	0,1218	0,0064	0,0012	0,0008	0,0004
UGT1A4	rs377453564	Intronic	Modifier	0	0,0001	0,0001	0,0001	0,0002	0
UGT1A4	rs3821242	Intronic	Modifier	0,3684	0,6401	0,4537	0,3342	0,4453	0,61
UGT1A4	rs4148323	Intronic	Modifier	0,0172	0,0009	0,026	0,1524	0,0036	0,019
UGT1A4	rs45449995	Intronic	Modifier	0,0159	0,0485	0,0165	0,0018	0,0306	0,0193
UGT1A4	rs570829500	Intronic	Modifier	0	0,0003	0,0002	0,0001	0	0
UGT1A4	rs62191918	Intronic	Modifier	0,1016	0,0946	0,1192	0,2103	0,0615	0,1818
UGT1A4	rs6431625	Intronic	Modifier	0,4531	0,6698	0,3398	0,1206	0,3867	0,4283
UGT1A4	rs6706232	Intronic	Modifier	0,582	0,7644	0,4583	0,3345	0,4473	0,61
UGT1A4	rs7574296	Intronic	Modifier	0,5192	0,7646	0,4587	0,3322	0,4478	0,6098
UGT1A4	rs77053267	Intronic	Modifier	0	0,0149	0,0004	0,0001		0,0001

Table 2 presents all variants identified in the indigenous population in a detailed manner, including: gene, refseq, dbsnp, VarType, Impact and detailed region.

Table 2. - Description of variants found in the indigenous population.

Gene	Refseq	dbSNP	Var Type	Impact	Region Detailed
CYP3A4	NM_017460.5	.	SNV	LOW	SYNON_COD

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SULT2A1	NM_003167.3	rs11569678	SNV	MODIFIER	UTR_3_PRIME
SLCO2B1	NM_007256.4	rs12287059	SNV	MODIFIER	INTRON
SLCO2B1	NM_007256.4	rs12422149	SNV	MODERATE	N_SYNON_COD
UGT1A4	NM_007120.2	rs12466997	SNV	MODIFIER	INTRON
UGT1A4	NM_007120.2	rs12471326	SNV	MODIFIER	INTRON
CYP3A4	NM_017460.5	rs12721620	SNV	MODIFIER	INTRON
SLCO2B1	NM_007256.4	rs1944612	SNV	MODIFIER	UTR_5_PRIME
UGT1A4	NM_007120.2	rs2011404	SNV	LOW	SYNON_COD
SLCO2B1	NM_007256.4	rs2306168	SNV	MODERATE	N_SYNON_COD
SULT2A1	NM_003167.3	rs2547238	SNV	MODIFIER	INTRON
SLCO2B1	NM_007256.4	rs2851069	SNV	MODIFIER	UTR_5_PRIME
UGT1A4	NM_007120.2	rs28898618	SNV	MODIFIER	INTRON
HSD3B1	NM_000862.2	rs33937873	SNV	LOW	SYNON_COD
UGT1A4	NM_007120.2	rs3732217	SNV	LOW	SYNON_COD
UGT1A4	NM_007120.2	rs3821242	SNV	MODIFIER	INTRON
UGT1A4	NM_007120.2	rs4148323	SNV	MODIFIER	INTRON
UGT1A4	NM_007120.2	rs45449995	SNV	MODIFIER	INTRON
HSD3B1	NM_000862.2	rs6203	SNV	LOW	SYNON_COD
HSD3B1	NM_000862.2	rs6205	SNV	MODERATE	N_SYNON_COD
UGT1A4	NM_007120.2	rs62191918	SNV	MODIFIER	INTRON
SULT2A1	NM_003167.3	rs62531056	SNV	MODIFIER	INTRON
UGT1A4	NM_007120.2	rs6431625	SNV	MODIFIER	INTRON
UGT1A4	NM_007120.2	rs6706232	SNV	MODIFIER	INTRON
SLCO2B1	NM_007256.4	rs7125268	SNV	MODIFIER	INTRON
SLCO2B1	NM_007256.4	rs74885054	INDEL	MODIFIER	INTRON
UGT1A4	NM_007120.2	rs7574296	SNV	MODIFIER	INTRON

Through multidimensional scaling analysis (MDS) (Figure 3), using the FST values (supplementary table) for the 46 variants related to the genes SLCO2B1, SULT2A1, CYP3A4, HSD3B1, HSD3B2, and UGT1A4, the distribution of the five population groups was evidenced (Figure 2). Based on the distribution of populations, the African population is isolated, as expected due to genetic diversity. The American and European populations show significant similarity, followed by populations from South Asia and East Asia with little divergence. An important point to note is the indigenous population, which is also isolated from all other populations, indicating a significant genetic distance from them. The isolation of the studied Amazonian indigenous population contributes to the existence of the variant described only in this population.

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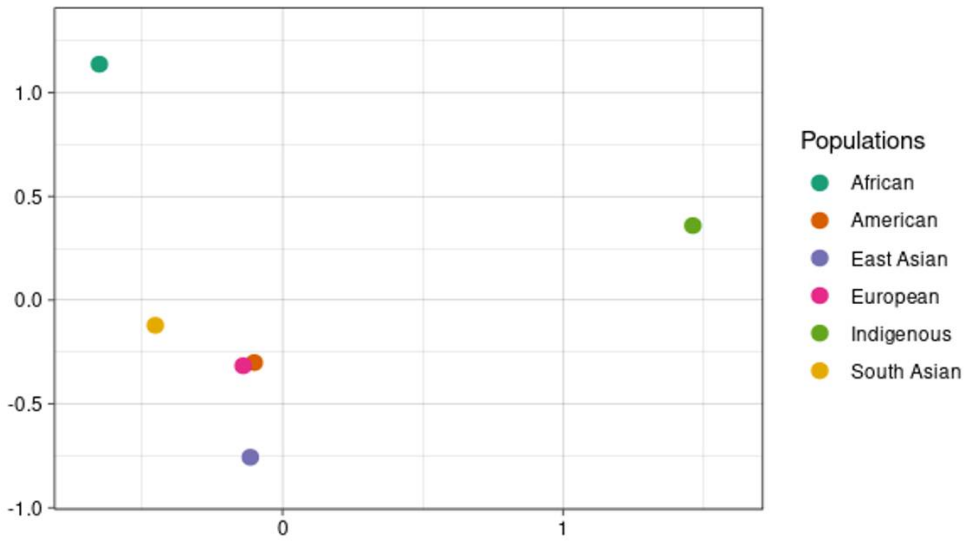

Figure 3. *Multidimensional scaling analysis (MDS).*

4. Discussion

According to the World Health Organization (WHO), in 2020 the global incidence of prostate cancer was 1.2 million individuals, ranking fourth in terms of the number of cases and resulting in 375,000 deaths. Despite its high incidence, the survival rate is 78%, achieved through effective therapeutic approaches including early diagnosis and protocols based on androgen deprivation therapy (ADT) and prostatectomy procedures.

In cases with a poor prognosis, such as castration-resistant prostate cancer (CRPC), individuals may develop resistance to treatment despite adherence to protocols. This resistance often leads to high levels of steroid hormones, such as testosterone, even after ADT and prostatectomy protocols are implemented. Increased steroid hormone expression is a key indicator of CRPC progression and is associated with a shorter survival time.

To understand the mechanisms underlying resistance, genetic studies have focused on genes involved in steroid hormone regulation linked to CRPC incidence. Tissue analysis of these tumors revealed variants in the HSB3D1 gene, which plays a crucial role in steroid hormone production regulation. Due to the significance of this gene and the recurrent mutations observed in individuals with CRPC, it has been identified as a biomarker for poor prognosis in ADT protocols.

In accordance with the guidelines for prostate cancer management provided by the National Comprehensive Cancer Network (NCCN), the primary medication used for treating CRPC is abiraterone acetate. Building upon this protocol, an examination of mutations in this gene and other genes implicated in its signaling pathway was conducted, along with an assessment of the prevalence of these variants in global populations. Additionally, the study delved into the evaluation of these variants within indigenous populations of the Amazon, renowned for their extreme genetic isolation, which often yields divergent treatment responses compared to other populations, including heightened drug toxicity and diminished efficacy.

The distinctive and secluded genetic profile of the indigenous population is highlighted through the multidimensional scaling analysis (MDS) graph (Figure 3), where this population emerges as distinctly separate from others in terms of the identified variants within the studied genes. Notably, the population most genetically akin to the indigenous population is the American population, owing to greater amalgamation with Latino populations.

This genetic distinctiveness underscores the imperative for a highly tailored approach in precision medicine. Analysis of the variants present in the target genes revealed occurrences across all genes studied. For the HSD3B1 gene, three occurrences were identified, two initially classified as having low impact (rs33937873 and rs6203), yet recent studies indicate they serve as risk factors for prostate cancer development and recurrence. Additionally, a variant with moderate impact (rs6205) was identified.

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In the SLCO2B1 gene, seven variants were detected, all of which play a pivotal role in ADT protocols by facilitating the transport of abiraterone. Variants within this gene have been associated with cancer progression and poor response to ADT.

Among the five variants described in the SULT2A1 gene, three were found within the indigenous population, all characterized by a modifier impact. Variants within this gene have been linked to an increased risk of prostate cancer development.

The gene harboring the greatest number of described variants within the studied pathway was UGT1A4, with twenty-six variants described, ten of which were identified within the indigenous population. These variants have been associated with the recurrence of localized prostate cancer following radical prostatectomy.

The CYP3A4 gene exhibited the fewest occurrences, with three detected across all studied populations and two within the indigenous population. One occurrence pertained to a new variant lacking description within the examined databases, initially classified as having a low impact. This discovery underscores the genetic distinctiveness of the Amazon indigenous population, as evidenced by the multidimensional scaling analysis (MDS).

Overall, the indigenous population lacks the variant associated with HSD3B1-mediated CRPC, suggesting a potentially more favorable prognosis for prostate cancer treatment. However, variants indicating a risk of developing this type of cancer were uncovered, accentuating the importance of implementing strategies for early diagnosis to enhance treatment efficacy. The identification of a new variant within the CYP3A4 gene underscores the uniqueness of the Amazon indigenous population in genomic studies, rendering this study singular in its field.

These findings and discussions contribute to the development of novel clinical protocols for precision medicine in hormone therapy, aimed at facilitating more efficacious management of this population and mixed populations.5. Conclusions

This section is not mandatory but can be added to the manuscript if the discussion is unusually long or complex.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org

Conflicts of Interest: The authors declare no conflicts of interest.

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