

The Human Population Genetics at State of Rondônia - Brazil

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Published Date: July 26, 2017

ABSTRACT

The State of Rondônia makes 6,16% of North Brazilian region and is located in Amazonia rainforest, bellow of Equator line. Its human occupation remains at century XVIII with the poses of amazona basin by the luso-brazilians to protect brazilian lands of invasion by french, dutch and Spanish. After the invention of rubber’s vulcanization, at 1839th, there was two so called “rubber boom”, when European descendants formed many small riverine settlement along the banks of the main rivers. Anothers sources of migration was the construction of the Madeira-Mamoré railroad andwhen federal government offered free land to a large contingent of settlers from the southern states of the country. Northeastern Brazilian, makes a important african genescontributing, too. At last years, there was another great migrations,at least 80,000 people arrived in the State of Rondônia, attracted by new jobs opportunities at the construction sites of the Jirau and Santo Antônio hydroelectric power in municipalities of the state’s capital city of Porto Velho. These migrations área allowed that the local indigenous populations mixed with European and African descendentes, and those two last insider itselfs, making then a characteristic thihybride population. These work intends to summarize the knowledge of the gene dynamics at human population by State of Rondônia.

These population has characteristics like a great genetic variability, thi-hybride ethnic composition and is exposed to environmental pressures caused by the large number and frequency of parasitic infections. There are few epidemiological and genetic datas at the Rondônia's populations making very importante to carry out more studies that address the genetic factors that modulate the most prevalent susceptibility in the region, that affect populations at the endemic level.

Keywords: Amazon Populations; Epidemiology Studies; Ethnic Admixture; Small Communities; Genetic Markers; Parasitic Disease.

INTRODUCTION

Brazil, the sole Portuguese-speaking nation in the Americas, is also largest country in both South America and Latin America, besides being the largest of the Americas by continental area (8.515.767,049 km²) [1]. Its history begin at 1500 when Pedro Alvares Cabral, a Portuguese nobleman, military comande, navigator and explorer discovered Brazil's land and claimed to Portugal Empire.

This coutry is a federation composed of 26 States and one Federal district grouped into five regions: Southern, Southeast, Central-West, Northeast and Northen. These regions are merely geographical, not political or administrative divisions.

The Northen region is located in Amazonia rainforest and is the largest, corresponding to 45.27% of the national territory with the lowest demographic density (3.8 inhabitants per Km²) in the country. It comprises seven Brazil's States, one of then the State of Rondônia [1].

Brazil was inhabited by numerous tribal nations prior to the Portuguese colonization. A considerable miscegenation between Amerindians, Europeans (mainly portuguese), and Africans has taken place in all regions of the country, but at North region the amerindian contribution to former this population is highest than others four regions [2].

We reviewed primary scientific articles that analyzed the genetic polymorphism at human population from State of Rondônia. A bibliographical search was performed using the PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>) and Periodico CAPES (<http://www.periodicos.capes.gov.br/>)-a virtual library, maintained by MEC (Ministry of Education of Brazil). The search was limited to studies published between 1984 and 2017. Also, were included thesis, the most of them by researchers linked to Experimental Biology Program (<http://www.pgbioexp.unir.br/?pag=downloads>), a post- graduated course from University of Rondônia and recomended by CAPES (Coordination for the Improvement of Higher Education Personnel (Capes), founding of the Ministry of Education (MEC), Brazil).

Here we will show relates from studies that reports of gene frequency, association analyses or evolutionary studies at human populations from State of. Also, an brief review on Brazilian State

of Rondônia history is shown to assist in understanding the pattern of population migrations and population structure.

BACKGROUND

Brazilian State of Rondônia, Occidental Amazônia

The State of Rondônia (Figure 1) makes 6.16% of North Region and is bellow of Equator line, crossed by the parallel of 10° South and standing between the meridiano of 60° and 65°. Border with Amazonas State, Mato Grosso State, Acre State and Bolivia country. Its human occupation remains at century XVIII with the poses of amazona basin by the luso-brazilians to protect brazilian lands of invasion by french, dutch and Spanish [3].

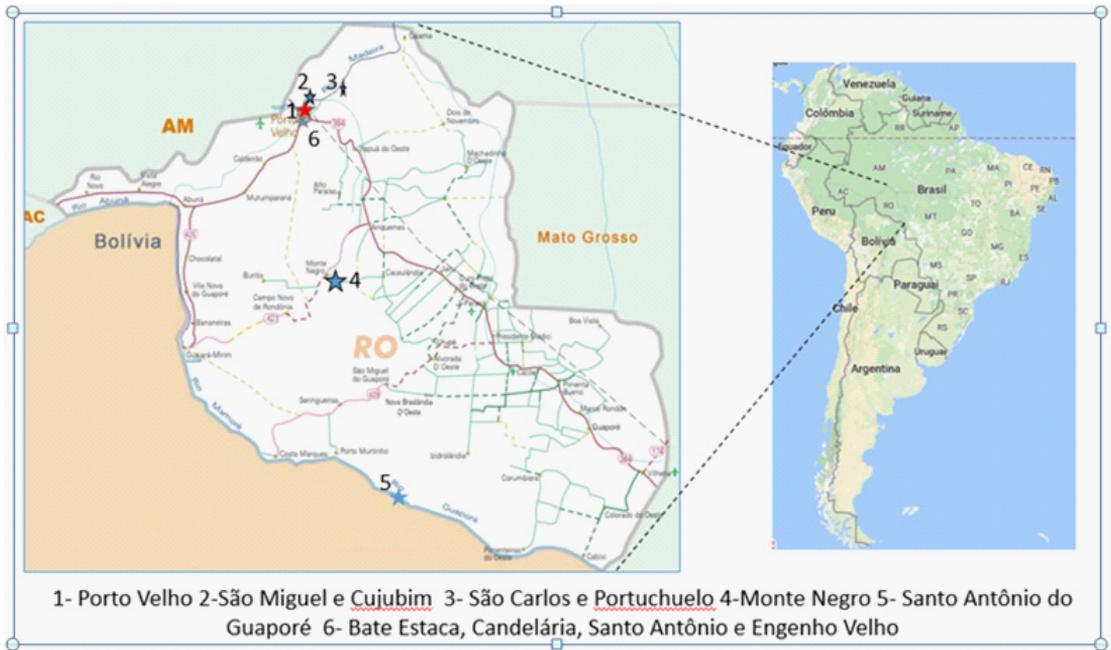


Figure 1: State of Rondônia and approximated geographical localization of the sampled population. (modified from www.googlemaps.org and <http://www.mapas-brasil.com/rondonia.htm>)

After the invention of rubber’s vulcanization, at 1839th, there was the first so called “rubber boom”(1877-1912). Once Rondônia had a lot of *Hevea brasiliensis* trees (produce natural rubber) there was a first great human migrations to State. European descendants formed many small riverine settlementat rivers Madeira, Mamoré, Guaporé, Machado and their tributaries. Another source of migration was the construction of the Madeira-Mamoré railroad. With these two factors there was an approach of european descendants comes from South and Southerst Brazilians region, Northeastern Brazilian, with a strong african genes contribution by their Bantu and Sudanese slaves descendents, and also Caribbean workers, particularly from Granada and Barbados [3-5].

Between 1912th and 1942th there was a great decrease of migration, with some peoples going out for Rondônia, looking for another better life opportunities. The second “rubber boom” was after Brazil and United States of America signed the treaty, in 1942th, encouraging the latex’s extraction in the Amazon. At this time the migration was basically from Ceará’s inhabitants, from Brazil’s Northeast, who have a great African genes contribution. With the end of Second World War, and low price of rubber, the migration stopped again [3].

After, there was a third migration, around 1970s and 1980s, when federal government offered free land to a large contingent of settlers from the southern states of the country. These migratory waves were occurred in concordance with four major malaria epidemics have been recorded in the region of the State of Rondônia [6].

Malaria is one of the tropical diseases that most affect human health in the Amazon, and has a negative impact on the State of Rondônia and the Amazon region as a whole. Environmental changes caused by human activities that favor the proliferation of *Anopheles darlingi*, malaria’s main vector, is one of factors that contribute to the occurrence of malaria in the State of Rondônia. The improvements in the financial and social conditions of the population of Rondônia represent improvements in the population’s quality of life and a reduced rate of exposure to infection risks [7].

In the last time, early 2000’s, it was estimated that at least 80,000 people arrived in the State of Rondônia, attracted by new jobs opportunities at the construction sites of the Jirau and Santo Antônio hydroelectric power in municipalities of the state’s capital city of Porto Velho [8]. Katsuragawa et al [9] analyzed malaria prevalence before the construction to provide information on the possible impacts of malaria burden related to the migration and according to their findings, once there are the existence of potential asymptomatic malaria carriers among the local population was epidemiologically relevant to be considered in the malaria control programs organized by public authorities and companies responsible for building the power plants.

The report of the public ministry of Rondônia recommended a series of activities to be taken by the company responsible for the construction of the hydroelectric dams in order to protect the ecosystem, to prevent organized crime in the impact region involving the states of Rondônia and Amazonas and, besides others, the need for increase studies on public health and suggesting the execution of programs such as control of endemics, infectious diseases and sexually transmissible diseases and other relevant points [10].

A study that evaluated the epidemiological profile of malaria in Rondônia between 2008 and 2012 showed a 58% reduction in the number of malaria cases and a 36.2% reduction in the number of relapse/recrudescence malaria cases, due to increases in the economy, improvements in the health system, and reduction of deforestation in this region [7].

There are other diseases that are considered endemic and as an important public health

in Rondônia. For example can be cited infection with hepatitis B virus (**HBV**) where that was observed 9 of the 52 municipalities of Rondônia exhibiting an incidence > 40/100,000 inhabitants, and the high incidence rates are progressively increasing [11]. Also, American Leishmaniose Tegumentar (**LTA**) is endemic at State of Rondônia [12], though there are literature showing the decrease of this disease in the last years in some municipalities of Rondônia [13].

The knowledge about gene frequencies and precise estimates of ancestral proportions in mixed populations have been used to answer questions related to anthropological evolution and the effects of population substructure in association studies. In epidemiological studies with case-control design, ethnic heterogeneity between subgroups can produce false positive results. By defining the levels of population structure in groups and subgroups may optimize their design to avoid this undesirable findings. Ethnic differences may reflect the assortment of favorable genetic mechanisms involved in the resistance/susceptibility to specific infectious/ecological diseases [14].

ANALYSIS OF THE GENETIC POPULATION STRUCTURE

Before talking about the structure genetic, is importante define some characteristics of the populations who was sampled, because the mostly studies was made in a little number of non indigenous communities (Table 1).

Table 1: Characterization of the Studied Groups from Rondonia State, Brazil.

	Geographic coordinates	Socioeconomic status	Reference
Bate Estaca	8° 47' 2" S, 63° 54' 14" W	Urban/riverine	[21]
Candelária	8° 47' 18" S, 63° 55' 00" W	Urban/riverine	[38]
Cujubim	8° 45' 43" S, 63° 54' 14" W	Riverine	[2]
Engenho Velho	8° 47' 38" S, 63° 56' 41" W	Urban/riverine	[38]
Monte Negro	10° 15' S, 63° 18' W	Rural county	[4]
Porto Velho*	8° 45' 48" S, 63° 54' 48" W	Urban	[2]
Portuchuelo	8° 37' S, 63° 49' W	Riverine	[4]
São Carlos	8° 39' 44" S, 63° 49' 14" W	Riverine	[38]
Santo Antônio	8° 48' 35" S, 63° 56' 34" W	Urban/riverine	[38]
Santo Antônio do Guaporé	12° 32' 33" S, 63° 31' 37" W	Riverine	[2]
São Miguel	Left bank of the Madeira river	Riverine	[2]

* Porto Velho City is the capital of State of Rondonia.

Tupí linguistic groups display a wide geographical dispersion in South America. Based on the huge linguistic diversity of the Rondonian Tupians, archeological records as well as genetic data on Tupí populations, their geographical origin is proposed to be at the State of Rondônia. Moreover, the comparative analysis of biparental and uniparental markers also provided clues about the migrational patterns of men and women. The genetic differentiation between Amerindian populations was higher for Y markers than for mitochondrial and autosomal ones, being suggestive of patrilocality [15].

Amerindians has some singularities at their genetic frequencies as showed in some studies. Ellis et al [16] studing human evolution by investigation of the boundary between pseudoautosomal and sex chromosome-specific regions by examining the population structure of an polymorphim (XY274, assigned by low and high alleles), in 9 world populations, found that only in the two amerindians populations come from Rondônia (Surui and Karitiana), the high allele appears fixed on the Y chromosome.

In a human molecular diversity analysis at 109 DNA markers (STR and RFLP polymorphisms) in 16 populations of the world by partitioning genetic variances at three hierarchical levels of population subdivision (from small communities to very large regions) found that, differences between members of the same population account for 84.4% of the total. Genetic variation in repeat number for Surui of Brazil was (1.44 differences) the lowest value founded [17].

About not indigenous population, the mean allelic diversity, using STRs systems in two riverine population belong at Porto Velho city, was between 6.97 [18] and 8.0 [19]. According to Krauze [18] the allelic diversity at european, african and indigenous populations, respectively, range 6.75- 8.5. 8.25-8.25 and 5.5-5.5. The same authors shows values from observed and expected heterozygosity at that populations (Table 2).

Table 2: Heterozygosity (observed and expected) into four small riverine population around Porto Velho city (State of Rondônia) measured by STR markers.

Population	n	Markers	Observed Heterozygosity (Ho)	Expected Heterozygosity (He)	Ref.
Bate Estaca	24	HUMCSFPO1	0,542	0,605	[18]
		HUMTPOx	0,708	0,740	
		HUMTH01	0,707	0,756	
		vWA	0,792	0,802	
Candelária	83	HUMCSFPO1	0,614	0,605	[19]
		HUMTPOx	0,723	0,748	
		HUMTH01	0,867	0,796	
		vWA	0,759	0,783	
São Miguel and Cujubim	80	FGA locus	0,629	0,747	[19]
		D3S1358	0.75		

Observed genic and genotypic distributions at HB, CCR5, CYP2E1, GSTP1, GSTT1, ACP1 loci and eight alleles from CFTR gene ($\Delta F508$, N1303K, W1282X, G551D, R553X, R1162X, G85E e R334W) showed that analysed population on those studies do not differ, by frequency patterns, from others brasilian populations [20-23]. Another data when compared with those from African, Amerindian and European populations have shown no significant genetic distance between northern Brazil populations and Europeans, but there is a significant genetic distance when compared to Africans and Amerindians [24]. Phylogenetic analyses between four communities (an large urban and three riverine small communities, one of know be a quilombo's remnant) shows the proximity of them with Spanish and Portugal populations [2].

The most of pappers classified the ethnic classes population by autosigned skin collor. Sometimes, the people who is collecting the datas assign the sampled individual by appearance (streight hairs x curley hairs; skin collor, lips format, and stuff). Usually, this kind of data is grouped on withe, parde (or mixed or “mulato”), negroes and yellow (for indians ancestral) people [25-28].

Datas indicates the indigenous population contributing to genetic formation of Porto Velho populations. This is the case found at NAT2*7B allele, responsible for low acetylation at Amerindians, and founded at hight frequency at that population and was found at 11.52% frequency at na urban sample of Porto Velho population [27].

There are a few ethnic admixture studies about Rondônia population. Pearce-Silva et al highlights the multi-ethnic profile of the Porto Velho population [28]. These profile is assign by comparative data and skin collor observed from sampled populations individuals. One of theses analyses suggest that the most strong fator inside Porto Velho city formation was the negrous and indigenous genetic contribution. The history of this city is in accordance with this point [29]. But resultados from ethnic admixture calculations (see table 2) suggest, in the most cases, that the major gene contributions was by european, followed by africans and indigenous (Table 3). Exporadically there are some relates about gene contributions from anothers ethnic populations [25].

Table 3: Ethnic admixture in some state of Rondônia populations.

Population	Kind of markers	Gene componente				Ref.
		African	Amerindian	European	Other	
Porto Velho	GYPB'S/s	0,18±0,14	0,28±0,17	0,54±0,19	--	[34]
Porto Velho	Y haplotype	0,079	0,005	0,849	0,066*	[2]
Porto Velho	DNAm ^{***}	0,17	0,25	0,54	0,04*	[2]
Bate Estaca	STRs	0,22±0,06	0,16±0,03	0,62±0,07	--	[18]
Candelária	STRs	0,37±0,16	0,05±0,08	0,58±0,18	--	[18]
Cujubim	Y haplotype	0,059	0,006	0,705	0,235**	[2]
Cujubim	DNAm ^{***}	0,684	0,263	--	0,053#	[2]
São Miguel	Y haplotype	0,167	0,0021	0,831	0,003	[2]
São Miguel	DNAm ^{***}	0,125	0,87	--	--	[2]
Monte Negro	classic	0,25±0,032	0,12±0,046	0,63±0,054	--	[4]
Portochuelo	classic	0,21±0,046	0,44±0,064	0,35±0,069	--	[4]
Portochuelo	STRs	0,12±0,059	0,32±0,087	0,56±0,106	--	[44]
Santo Antônio do Guaporé	Y haplotype	0,499	0,008	0,499	0,001	[2]
Santo Antônio do Guaporé	DNAm ^{***}	0,65	0,20	0,15	--	[2]

* 0.04 undetermined; ** 0,176 undetermined; *** mitochondrial DNA haplotype (HVI region) # undetermined.

The ethnic admixture based on paternal and maternal haplogroups indicate that the European contribution was greater on paternal sides, and maternal sides was made from the three or two ethnic contributions. The exception was found at Santo Antonio do Guaporé, where paternal contribution appears to be equally from European and African.

GENETIC TRAITS

Little is known on the genes frequency at population from State of Rondônia. The most of studies found are reporting alleles frequencies in Porto Velho city or small riverine populations nearest the capital city. Genetic frequencies data are available for some other small communities [2,4,30]. Some indigenous genetic frequencies are available only for four (Surui-ALFRED UID:PO000014F; Karitiana-ALFRED UID:PO000028K; Gavião-ALFRED UID:PO000127K and Cinta Larga-ALFRED UID:PO0004820) among nine indigenous ethnic living at State of Rondônia at ALFRED (The ALlele FREquency Database; <http://alfred.med.yale.edu>) [15].

The geographical origin of Tupí linguistic group was settled by comparative analysis of biparental and uniparental markers and allowed to approach the genetics point of view. In accordance with the Tupians archeological records, linguistic diversity and the ancient human occupation of Rondônia, the genetic analyses propose to be at southeast of Amazonia, at the Brazilian State of Rondônia, their geographical origin. Additionally, the comparative analysis of biparental and uniparental markers also support that the genetic differentiation between Amerindian populations was higher for Y markers than for mitochondrial and autosomal ones, being suggestive of patrilocality. This hypothesis is made strong by the fact of patrilocality and agriculture are associated in many human populations [15].

ASSOCIATION AND LINKAGE STUDIES

Ethnicity may be an important variable helping to explain inconsistencies that have been reported by association studies [31]. The following are listed works aimed at the epidemiological-genetic study of infectious-parasitic diseases.

Genetic Polymorphisms and Malaria

Malaria illness is, most likely, the principal aim of epidemiological researches at State of Rondônia. In 2011, the district of Porto Velho in Rondônia was the second district with the highest number of cases in the Americas.

When Cavasini et al [32] compared Duffy blood group genotype distribution, determined by allele-specific PCR, in Plasmodium vivax-infected patients and non-vivax malaria controls from Rondônia their results don't agree with the hypothesis that heterozygosity for the wild-type erythrocyte-specific promoter of the Fy gene may confer some protection against P. vivax infection. Instead, by thirteen genetic blood polymorphisms investigated in 182 individuals belonging to Portuchuelo, a riverine population of State of Rondônia, authors indicated that the Duffy system

is associated with susceptibility to malária. Moreover, suggestions also indicate that the EsD and Rh loci may be significantly associated with resistance to malária [33].

SNP's in the genes immune response Ser180Leu TIRAP polymorphism has a significant pattern for the number of malaria infections throughout life, showing a decrease in the average rank of infections. Heterozygous and mainly homozygous for the SNP TLR1 602 have the ability to make individuals less susceptible in the development of malaria infestations [25].

Epidemiological and evolutionary approaches suggest an important role for the GPB receptor in RBC invasion by *P. falciparum* in Brazilian Amazons. In a Porto Velho city sample results suggest that the S domain on GPB is important for its binding to the specific ligand of the *P. falciparum* parasite, EBL-1, which was recently identified and characterized [34].

Mendonça et al [35] investigate the relationship between single nucleotide polymorphisms (**SNPs**) in the DDX39B, TNF and IL6 genes and the clinical outcomes of patients with *Plasmodium vivax* malaria. This study was performed with participants living in riverine communities of the state of Rondônia (n=257) plus a sample of patients with either mild signs/symptoms of acute malaria (mild malaria, n = 69) or clinical complications recruited from the state of Amazonas in the Western Brazilian Amazon. They found that the C allele of DDX39B-22C >G is a potential risk factor of complicated vivax malária in the Brazilian Amazon.

There are a study that shows that the IL10A-592A/C and IL10A-819 T/C polymorphisms were associated with malaria and decreased IL-10 levels and low parasite density suggesting that this polymorphism influence IL-10 levels and may influence in the susceptibility to clinical malária [36].

No genetic correlations between malária susceptibility or *Plasmodium infection* (*P.falciparum* and/or *P.vivax*) was observed in populations from State of Rondônia for G6PD locus [37], IFNG+874 T/A, MBL2 [38], GSTP1, GSTT1 [20], KIR genes [28], and NOS2A-954G/C [36].

Tuberculosis (TB)

At State of Rondônia there was notificated, between 2000 and 2004, 3,237 cases of this disease, with a anual average of 647 cases, grouped in 87% with pulmonary TB clinical form, 11,10% with extrapulmonary form and 1,68% both, pulmonar and extrapulmonary TB form. The number of TB cases has been constant among the years, who shows that this infectious disease are not under control in the region [39]. From 265 patients with tuberculosis from Porto Velho city, between 2008-2009, 14.3% showed serius imperfections in basic informations of the patients' illness, resulting in a total of 227 hold good records. Among these, 84.2% had lung TB localization, 7%, was extra-lung localization and in 6.8% records do not show this kind of TB classification[40].

In studies at Porto Velho city TB patients populations it was not found positive associations related with ções positivas GSTM1 [26] and A1AT [40] genes. At the same populations was found that a GSTT1 null phenotype to confer statistically significant protection against TB (OR = 0.4315.

CI = 0.2218 - 0.8395. $p = 0.0172$) [26]. But, these data are different from those shown in other study related to respiratory diseases at Russian [41], indicative that more research is needed, particularly at Brazilian population, to confirm the association of these polymorphisms with such diseases.

Individuals diagnosed with TB are from two local studies that have analyzed separately the same individuals for genetic variants of GSTs (M1 and T1), ACE and eNOS. The genotype combinations made of 2 on 2 and 3 on 3 genetics systems proved to be statistically significant ($p < 5\%$) indicating a possible biological significance of the interactions between these genetic variations [42].

Genetic Polymorphisms and Hepatitis Virus

The Amazonia is one of the regions who have the highest rates of infection by Hepatitis B virus (HBV) in the world. In an epidemiological data shows that the average incidence rate in Rondônia is 42/100,000 inhabitants per year, and the municipalities with the highest incidence rates were Monte Negro (187.6/100,000 inhabitants) and Ariquemes (157.2/100,000 inhabitants). The young adult group (20-39 year-old) display the highest number cases. The major patients were likely infected via sexual contact and are in chronic phase. There was an increase of 402% in this disease at state of Rondônia [11]. We can't find any correlation data about HBV and genetic populations characteristics in literature.

Leprosy

The result of association study between the SNPs associated with slow acetylation phenotype and the occurrence of Dapsone's adverse reactions was found not significant [27].

Leishmaniasis

The familial distribution of the response to an antigenic extract of *Leishmania* (Montenegro skin tests was used) was analyzed by applying genetic epidemiology methods at a small rural Community in the inner of State of Rondônia, to measure the relative importance of genetic components in the expression of the studied characteristic. The results of analysis suggested the existence of a significant familial aggregation with strong genetic component. Complex segregation analyses support the suggestion and shows that the best model to explain the phenotype transmission in that population was the monogenic recessive one [43].

CONCLUSION

The human population from State of Rondônia has same characteristics like a great genetic variability, tri-hybrid ethnic composition and is exposed to environmental pressures caused by the large number and frequency of parasitic infections, mainly malaria, hepatitis B type virus, Leishmania infections, and so on. There are nine indigenous ethnic people at this state and the migration from other Brazilian regions is "like periodic" and associated with government-sponsored economic events. Epidemiological and genetic data at the Rondônia's populations

are few, and exist usually only with the same populations, mainly sampling Porto Velho city and its small riverine communities and around on Monte Negro, the small rural community.

Know the peculiarities of genetic structure of each population is importante to describe the migration effect and avoid non real associations in epidemiologic analyses. Is very importante to carry out more studies that address the genetic factors that modulate the most prevalent susceptibility in the region, that affect populations at the endemic level.

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