European father, African or Indigenous mother

DNA sequencing of 2,723 Brazilians reveals a violent legacy behind the interracial mixing that shaped the Brazilian people

MARIA GUIMARÃES __ photos **LUIZ BRAGA**

tradução

Unsurprisingly, Brazilian people have a mixed racial background, but the details of how this story unfolded and its consequences are only gradually being revealed by geneticists and historians. The latest study, which was published in the scientific journal *Science* in May, deepened and expanded our knowledge of Brazilians using the DNA sequencing of 2,723 people from across the country. The results reveal strong African and Indigenous ancestry in the maternal lineage, the legacy of widespread violence against women, and an unexpected number of unknown genetic variants with potential health consequences.

"It is really amazing to see in DNA what we already knew from history books," says geneticist Lygia da Veiga Pereira of the Institute of Biosciences at the University of São Paulo (IB-USP), creator of the "DNA do Brasil" project, which aims to paint a genomic portrait of the Brazilian population by sequencing complete samples collected from all over the country. According to Pereira, until approximately 10 years ago, the genetic diversity of human population samples was very low, around 80% from European ancestry, because most studies were carried out in the Northern Hemisphere. In Brazil, the focus was on the southern and southeastern regions, where a lower presence of African and Indigenous ancestry was found. Investments in expanding this perspective led to the Genomas Brasil Program at the Ministry of Health's Department of Science and Technology (DECIT) at the end of 2019, —although the COVID-19 pandemic, which started just a few months later, put a halt to activities for almost two years.

Pereira began to take an interest in the genetic diversity of the population when she realized, approximately 20 years ago, that the discarded embryos from assisted reproduction clinics in São Paulo that she used for her stem cell research were of 90% European ancestry. Those data were not representative of Brazil's makeup as a whole; it rather reflected the users of those private services. Meanwhile, geneticist Sérgio Pena of the Federal University of Minas Gerais (UFMG) was studying the DNA of Brazilians from various regions using the tools available at the time, which were much more limited than those in use today. In 2000, he published the results of an analysis of 200 samples from white people in *Ciência Hoje* and the *American Journal of Human Genetics*.

Interracial mixing in history

Violence in the formation of the Brazilian people left marks on the genome

1500

On their arrival, Europeans found a population of around 10 million Indigenous people, which was later decimated; sexual violence against women was the norm from the start

17th Century

Genetic markers from 16 generations ago show evidence of mixing between Indigenous women and European men

18th Century

The diamond mining period, which was almost 12 generations ago, brought a large influx of Europeans to Brazil; trafficking of slaves from Africa increased tenfold

Early 19th century

Before the end of the slave trade, around two million slaves were brought over from Africa in the 19th century; eight generations ago was the period of greatest mixing between men of European ancestry and women of African descent

1822 - Independence

Marriages between freed slaves and Europeans were encouraged as a "civilizing" strategy: there was talk of Europeanizing the mixed-race population

1850

Slave trafficking was prohibited

1871

The Law of Free Birth allowed children to be exploited up until the age of 21 but made it illegal for them to be sold. With the loss of market value, slave masters no longer had an interest in having children with enslaved women, and thus interracial mixing declined

1888

Slavery was abolished

Late 19th century, early 20th century

The Brazilian government encouraged the immigration of White men, especially Italians, Germans, Spanish, and Portuguese. The arrival of some four million Europeans is detectable in the genetic makeup

21st century

Most marriages are now between people of similar ancestries

SOURCE NUNES, K. *ET AL*. **SCIENCE**. 2025

Three in five had Indigenous or African maternal heritage, which was more than expected. The study was reported on by *Pesquisa FAPESP* in just its second year.

Pena continued to study the topic in more depth and joined forces with another group that was pioneering the study of Brazilian DNA, under the leadership of geneticist Francisco Salzano (1928–2018) of the Federal University of Rio Grande do Sul (UFRGS). Through research led by Maria Cátira Bortolini, which included Tábita Hünemeier's master's degree, the two groups from Minas Gerais and Rio Grande do Sul realized that the African contribution was much broader than indicated by historical records on slavery, which were highly concentrated in Angola, on the west coast of the continent. The western region, where Senegal and Nigeria are located, also made a significant genetic contribution—more in São Paulo than in Rio de Janeiro, indicating asymmetries in the slave trade, according to an article published in the *American Journal of Biological Anthropology* in 2007. "There is no other country in the world with as much interracial mixing as Brazil," Pena said in an interview in 2021.

INFOGRAPHIC ALEXANDRE AFFONSO / PESQUISA FAPESP MAGAZINE

The technology has since evolved significantly, leading to a new article published in *Science*. The paper reveals that European heritage accounts for approximately 60%, whereas African ancestry contributes 27% and Indigenous ancestry represents 13%, in addition to the sexual asymmetry noted by Pena: the paternal lineage, expressed on the Y chromosome present only in men, is predominantly (71%) European. Moreover, the DNA of the mitochondria—the part of the cells passed down only from the mother—comprises 42% African ancestry and 35% Indigenous ancestry. "The only explanation is four centuries of various forms of violence," summarizes Hünemeier, currently a professor at IB-USP and one of the leaders of the research. She notes that it is not uncommon to hear older people say things such as "my grandmother was caught by the lasso," without thinking about what this statement actually means. In more recent generations, marriage between similar ancestries has become more common. According to Hünemeier, the results help debunk the myth of racial democracy that is so often cited as part of the Brazilian identity, since interracial mixing was often something that occurred without consent.

"Brazil needs to reexamine its history and stop saying that we are a country of voluntary interracial harmony," adds USP historian Maria Helena Machado, who did not participate in the study. "Our mother is African, our grandmother is Indigenous, and our grandfather is a European who had illegitimate children with her out of wedlock." Machado is an expert in gender and motherhood during slavery, a system that spanned the entire colonial period and the empire. In 2024, she published the book *Geminiana e seus filhos: Escravidão, maternidade e morte no Brasil do século XIX* (Gemini and her children: Slavery, motherhood, and death in nineteenth century Brazil; Bazar do Tempo) in partnership with historian Antonio Alexandre Cardoso of the Federal University of Maranhão. "Enslaved women—Indigenous or African—were at the service of their enslavers, making harassment and rape commonplace," he states.

Women were thus doubly enslaved—forced into being workers and reproducers. "The very bodies of enslaved women were colonized," Machado explained that Portuguese colonial policies and the policies of Brazil as an independent country from 1822 onwards always encouraged racial mixing and whitening. For example, in 1823, as a member of the constituent assembly, José Bonifácio de Andrada e Silva (1763–1838) argued for the formation of Brazilian people through marriages between White men and Afro-descendant or Indigenous women. This approach was part

of a "civilizing" project in which the Black population would be integrated into the European population. With slavery continuing until 1888, however, enslaved women remained subject to those who had control over their bodies. "All of this led to the situation that geneticists now describe," Machado concludes.

The wide diversity of African ethnicities, as Hünemeier has noticed since the beginning of her scientific career, is also interesting. People who would never have met in Africa because they lived in countries and communities separated by great distances were forcibly placed on the same slave ships and grouped together in slave labor. The objective was to group people from different cultures who did not even speak the same language to minimize the risk of them organizing to fight back against their "masters." The result is an amalgamation of an entire continent, which can only be found in Brazil. "It is the country with the most African ancestry outside of Africa," says the geneticist.

In addition to the initial influx of Portuguese from the sixteenth century onwards, European diversity is also high, with a significant flow of immigrants from Germany and Italy in the nineteenth and twentieth centuries, as well as from other countries in lower amounts. One interesting data point was 10 individuals of Japanese descent sampled in São Paulo who showed no signs of interracial mixing, thus revealing a highly restricted and recent contribution to the genetic makeup of the national population.

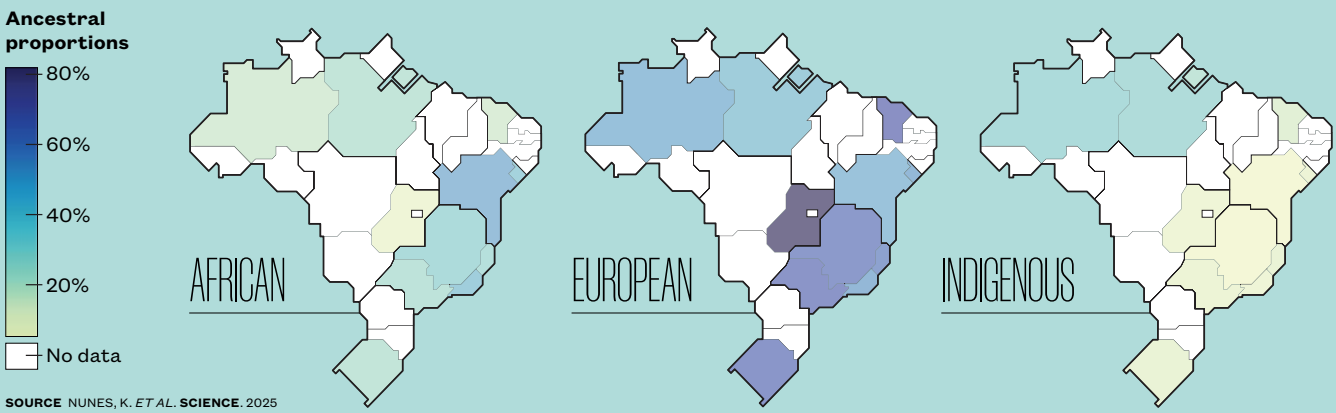
This article describes the colonization of the Americas as the largest population displacement in human history. In Brazil, some five million Europeans and five million Africans were transplanted to the region, which until then was populated by roughly 10 million Indigenous people who spoke more than 1,000 different languages. These peoples were decimated, suffering a population decline of 83% in the interior of the country and 98% on the coastline between the year 1500 and the present day.

"We expected to find new genetic variants, but the results went far beyond that," says geneticist Kelly Nunes, who analyzed the data during her postdoctoral fellowship in Hünemeier's laboratory at IB-USP, alongside three other colleagues with whom she shares the position of lead author of the article: Marcos Castro e Silva, Maira Ribeiro, and Renan Lemes. Variants are differences in a person's sequence relative to the reference genome. "We detected 78 million variants, of which almost nine million were not recorded in any other database." It became clear that the DNA of the Brazilian population includes a sample of populations that have been neglected from a genomic point of view, especially Africans and Indigenous South Americans. In the near future, with more sampling, it will be possible to better determine the scale of this source of genetic novelties. "We established partnerships to obtain samples from all five Brazilian regions, which gave us greater access to African and Indigenous ancestry," explains the researcher.

Approximately 36,000 of the nine million new variants described appear to have harmful effects by generating anomalies in their respective proteins, such as loss of function, and may be associated with diseases such as cancer, metabolic dysfunction, or infectious diseases. "What we discover about these variants can be extrapolated

Regional ancestry

The northeast of the country has more African areas, whereas the southeast and south are more European, and Indigenous heritage is more concentrated in the north



SOURCE NUNES, K. *ET AL*. **SCIENCE**. 2025

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to peoples that have not been sampled, such as those on the African continent," proposes Nunes. Knowledge of ancestry and how propensities for certain diseases are distributed across the genome and populations of the world can help make access to precision health more equal, as detailed in the article that follows this one on page 12.

When analyzing genes with signs that they were favored by natural selection (those that occur more frequently than would be expected randomly), many of those genes identified were linked to fertility or the number of children generated, with European ancestral origins. This trait clearly had benefits during the colonization process, during which the Portuguese who settled here quickly increased their presence. Immune response genes of African origin also showed signs of natural selection, reflecting the history of a broad range of pathogens.

The results also offer genetic clues concerning metabolic diseases concentrated in Indigenous ancestry, which are apparently linked to gradual changes in eating habits. "We started eating processed foods, which creates an environment of natural selection for certain genes," explains Nunes.

One of the study's challenges was the data analysis, which relied on cloud computing infrastructure provided by Google. "In Brazil, there were no professionals qualified to deal with this volume of information," says the geneticist, who claims to have learned a lot from the project, which also trained many other people. Another 7,000 genomes have already been sequenced, expanding the search for representation. The authors promise there will be new results soon.

Similar initiatives in other countries in the region could also contribute to our understanding of South American history. "We detected a specific component of pre-Columbian genetic ancestry, present mainly in central-western Argentina," Argentine geneticist Rolando González-José, a researcher at the Patagonian National Center (CENPAT) and head of the Argentine Population Genome Reference and Biobank Program (POBLAR), who is not a participant of the USP project, told *Pesquisa FAPESP* by email. "Long-held assumptions about population dynamics in the post-contact period do not sufficiently explain the evolutionary history underlying genetic diversity in modern Argentine populations." Collaborations with Brazilian scientists, in his opinion, can bear fruit. ●

The research project, scientific articles, and book consulted for this report are listed in the online version.

Precision for all

Genome information about the Brazilian population could democratize access to personalized treatments and reduce national health care costs

MARIA GUIMARÃES __ photos LUIZ BRAGA

Precision medicine was born out of human genome sequencing and is not a luxury—on the contrary, it enables more accurate diagnoses of some diseases and better and safer medication planning. It is good for the health care system, helping reduce wastage of resources on ineffective procedures, and it is good for patients, who receive the treatment that works best for them, with fewer side effects. However, Brazil suffers from a shortage of the biological parameters needed to know which genetic variants cause which diseases in the country because the sequences used as international references were mostly obtained from people of European descent in the Northern Hemisphere.

The focus on local and regional diversity is not parochialism. Although most of the genome is common to all people, specific modifications can make a significant difference in how genes function, and if defective, they can cause diseases). It is therefore crucial to understand the genetic composition of the Brazilian population, which is why the Department of Science and Technology (DECIT) at Brazil's Ministry of Health is now creating the National Genome and Precision Medicine Program: Genomas Brasil. In addition to examining Brazilian DNA (see report on page 6), it encompasses other projects, including Genomas SUS, through which several universities are evaluating the impact of the genome on health.

Started in April 2024, the project aims to sequence the complete genomes of 21,000 Brazilians by November. The goal is to reach 80,000 genomes over the next three years, ensuring the ability to sample a high diversity of ancestries. Additionally, FAPESP has announced a call for proposals to fund the sequencing of an additional 15,000 samples. The aim is to select smaller projects from among scientists who are not currently participating in Genomas SUS. "The foundation will provide a counterpart to the national research," explains Dr. Leandro Machado Colli of the Ribeirão Preto School of Medicine at the University of São Paulo (FMRP-USP), coordinator of the project. "Samples can be collected anywhere in Brazil, as long as the researchers are based in São Paulo."

He explains that the strategy adopted by Genomas SUS is to use short-read sequencing, which involves reading the genome from short sections of 150 base pairs, a more cost-effective method. With more complete sequencing to ensure context, the benefits are tangible. "Of the 21,000 samples we already have, we will sequence 200 using long-read technology as a more accurate

point of reference," says the researcher. Long-read sequencing uses larger sections containing hundreds of thousands of base pairs. In the effort to identify genes linked to diseases, determining the ancestry of each section of the patient's DNA is essential. "We will then know what a certain piece of genetic material in a certain geographic location might say about a person's health." The reason is that with sequencing—even the least precise form—it is possible to identify the locations of altered variants on each chromosome and to potentially link them to a propensity for diseases associated with them.

To ensure that the diversity born from interracial mixing is properly represented, Genomas SUS has nine anchor centers across the country: two of them are in São Paulo, and the others are in Rio de Janeiro, Minas Gerais, Paraná, Pernambuco, and Pará. "The Brazilian population has a large representation of peoples who mixed during the country's formation, including people of Indigenous and African ancestry," says geneticist Ândrea Ribeiro-dos-Santos, head of the only center in the North region, which is based at the Federal University of Pará and opened in September 2024. "In the Amazon region, Indigenous women were often welcomed into quilombola communities because they knew the secrets and ways of living in the forest," he explains, based on research results from his group, which identified the sexual asymmetry in genetic contributions.

Just like the center in the Northeast, the Amazon region's center does not yet have its own sequencing device; thus, the DNA molecules that it collects must be sent for analysis at other centers. To date, 1,800 samples have been sequenced, most of which are from Pará. However, this should change with the inclusion of other states in the region. "Two weeks ago, we were on a health mission in Amapá, where we collected samples in partnership with the state and municipal health departments and the Federal University of Amapá." Agreements with institutions in Amazonas and Acre are under negotiation, seeking to comply with mandatory ethics issues. The challenges in the region are significant: it can take days to reach some traditional communities, with travel by plane and car followed by days on a boat. However, it is in these remote locations that a unique wealth of the Brazilian territory is found: the genetic and cultural diversity of its human population.

Ribeiro-dos-Santos highlights the importance to the Brazilian national health system (SUS) of

understanding regional or rare genetic variants so that the system can implement treatment protocols for diseases such as diabetes and cancer. There is usually no single gene behind these diseases but a multitude of pathways that can cause dysfunctions in cell replication, leading to cancer, or in metabolism in the case of diabetes, and any altered part can trigger the disease. A successful medication is one that affects the root of the problem. "Without specific knowledge, the patient may die as a result of the treatment, or it may have no effect at all."

"It is important to know how we can use the genome to understand social inequalities and better diagnose complex genetic diseases," adds biologist Eduardo Tarazona of the Federal University of Minas Gerais (UFMG), head of the National Institute of Science and Technology - Genome Ancestry, Diseases, and Bioinformatics in Brazil (INCT-AncesGen) and one of the researchers leading Genomas SUS. "The less European a person is, the less scientists and geneticists know about their diseases."

One example is an international study in which Colli participated. This study mapped areas of the genome linked to kidney cancer susceptibility and was published in the journal *Nature Genetics* in 2024. "In previous phases of the study, Brazilian samples were not included out of fear that racial diversity would reduce the effectiveness of the association analysis," says the doctor. However, the opposite turned out to be true: when a Brazilian cohort was included in the analyses, a previously unknown genetic variant was found that was present in people of African descent.

When American geneticist Francis Collins, then director of the US National Institutes of Health (NIH), gave a lecture at FAPESP in 2014, geneticist Iscia Lopes-Cendes of the University of Campinas (UNICAMP) asked him about the idea of carrying out a population-wide genome project in Brazil. His response was that it was unnecessary since human genetic diversity was already well described. "He was completely wrong. North Americans don't understand that other Latin populations are not the same as Mexicans," she laughs, not convinced by the answer. In 2015, Lopes-Cendes founded the Brazilian Initiative on Precision Medicine (BIPMed). "It is the first genome database in Latin America," she says.

"We have a partnership with the Genomas Angola (GENAN) project, and we have already collected 750 samples," adds the researcher, who

is supervising an Angolan doctoral student on the project. Lopes-Cendes hopes to find genetic variants that have not yet been described and that could have practical uses in both countries, which have ancestral links as a result of slaves brought over during the colonial period.

"If there is a place where precision health care can be made available to everyone, it is in Brazil," she says. "We have SUS." She refutes the notion that the technology would be available only to rich countries and people. On the contrary, she believes that it can be an important tool for preventive medicine. "Personalized health care allows for more efficient treatments, at the right dosages, for the right people, with fewer side effects and lower costs."

Together with geneticist Thais de Oliveira, a postdoctoral researcher at her lab, she published an opinion piece in the journal *Annual Reviews of Genomics and Human Genetics* in January, emphasizing the importance of public databases of genome information about Latin American populations. Argentine geneticist Rolando González-José of the Patagonian National Center (CENPAT), head of the Argentine Population Genome Reference and Biobank Program (POBLAR), agrees. "It is important for governments to make agreements on connecting genome databases in the region," he suggested in an email to *Pesquisa FAPESP*. Like Colli, he says that short-read sequencing has benefits in regard to optimizing available budgets.

The DNA do Brasil project, which is part of the Genomas Brasil Program, aims to contribute to precision health by providing a detailed overview of Brazilian genetic variation. The pharmaceutical industry could also benefit from these advances. In 2021, USP geneticist Lygia da Veiga Pereira, the founder of the project, used the knowledge that she acquired throughout her academic career to create a startup called gen-t, now funded by FAPESP's Innovative Research in Small Businesses program (PIPE). "We are building a health, lifestyle, and multiomics data infrastructure with 200,000 genomes, which can be used by the industry to accelerate the search for new drugs," she explains.

The initiative could complement potential implementations of new strategies by SUS. "We are just at the beginning of understanding the impact of genomics on population health," says Colli. ●

All the research projects and scientific articles consulted for this report are listed in the online version.