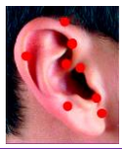
Scientists recorded the coordinates of a set of 18 facial anatomical landmarks around the lips, nose, and eyes. / Courtesy image



They also recorded the coordinates of eight landmarks on the ears. / Courtesy image

Cali's population is characterized by indigenous and mestizo communities, with components of Amerindian and African descent.

Living

The history of the human face shape

Colombian faces reveal details of some genetic syndromes

Estephania Candelo is a scientist from Cali who, together with other colleagues, is making an effort to fill a gap in the medical world: to demonstrate that there are differences in the faces of Latin American patients with certain genetic syndromes, which can lead to more accurate and timely diagnoses. Until now, the pattern of European faces had prevailed.

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The study of the human face has intrigued science for centuries. The answers to long-standing questions such as why we look one way and not another are not simple. Understanding the role of the face in our history is more complex than it seems. Think about the shape of your nose and its function: to capture air. Would it sound strange to think that over thousands of years the size of your nose has adapted according to the climatic conditions in which it captures oxygen?

Some interesting things are known about the nose. In 2021, a group of scientists led by Xiao-ming Zhang of the Chinese Academy of Sciences published an article in the *National Science Review* suggesting that wider noses are better suited to hot, humid climates, while narrow noses are better suited to cold, dry climates as they warm and humidify the air.

Is the environment, then, the only thing that matters when talking about the shape of a nose? It's not that simple. You only have to look at your photo album to know that genetics also determines our face. However, until very recently, scientists did not know which parts of our DNA are linked to the most basic aspects of our facial appearance. "That gap in our knowledge was particularly jarring," wrote on *The Conversation* two authors of a study that was published in 2020 in *Nature*, seeking to fill some of that gap.

There, the researchers scanned the DNA of more than 8,000 people for genetic clues to facial appearance: "This is a critical first step in understanding how genetics affects our face and how such knowledge could affect human health in the future," they noted.

Still, what do genetics and facial appearance have to do with health? A good way to understand this relationship is genetic syndromes, which often result from a harmful alteration in one or more genes. Syndromes such as Down syndrome, for example, cause particularities in areas of the face such as the nose, which can appear flat and with a very wide nasal bridge.

These facial patterns have been used by doctors to make diagnoses. Scientist Estephania Candelo, master in Genetics of Human Diseases and Tissue Engineering at the University College London, in the United Kingdom, knows this well: after graduating in Medicine from Icesi University, in Cali, she did her professional internship at the Center for Congenital Anomalies and Rare Diseases Research (CIACER) of her university.

There, Candelo discovered that detecting these facial characteristics has depended, to a large extent, on the experience of the physicians. Since it is not always the greatest (because, in addition, many of these syndromes are rare diseases), diagnoses arrive late. To prevent this from happening, doctors use automated systems. How do they do it? They base their diagnosis on the shape of the face.

In Europe and the U.S., the most widely used system is Face2Gene, an application that takes images of patients' faces and identifies similarities or features that could be related to signs of rare genetic disorders. Although it does not replace a physician's diagnosis, its efficacy is often high.

In January 2019, an article in *Nature* reported that the application achieved an average accuracy of 91% in identifying syndromes. To do so, the algorithm was trained on more than 17,000 images of confirmed cases of some 216 syndromes. Now, there was a small peculiarity: most of these images were from a population of European descent.

This reality led Candelo and a team from Icesi University, Valle del Lili Foundation [Fundación Valle del Lili] and the University of Barcelona to ask a question: Is Face2Gene efficient when it comes to diagnosing rare genetic conditions in populations of non-European ancestry, such as the Colombian population? What they really want to know is whether the facial characteristics of syndromes, such as Down syndrome, are the same all over the world or whether they differ from one another. The results of their research have just been published in *Scientific Reports*.

The distinctive face of Latinos

Every human face is unique. Even identical (or monozygotic) twins, who have very similar facial features and structures, have differences. Think of it this way: the face is made up of 14 bones and there are about 43 muscles involved in expressing more than 20 emotions. All those details develop around the fourth week of gestation, and their diverse variation is "complex and largely scientifically unexplained", a group of scientists wrote in a study published in the journal *PLOS Genetics* in 2014. They measured the face shape in people of mixed ancestry from West Africa and Europe and found that many parts of the face are affected by ancestry.

Ten simultaneous photographs of the entire face were taken./ Courtesy image

The study was awarded by the American Anatomical Association. / Courtesy image

If that past impacts the shape of our face, then the case of Latin America is mind-blowing. "We are a fascinating case of mixed population," says Candelo. The region began to be populated by migratory waves from North and Southeast Asia between 12,000 and 18,000 years ago, and during the last 600 years, with the Conquest, the mixture with European and African populations further shaped our genetic ancestry.

In order to understand this diversity, it will suffice to look at the case of Cali, Candelo's hometown. The population of Cali is the result of diverse migratory processes. The mixture with the indigenous Amerindian population began in the sixteenth century with the arrival of Spanish colonizers and in the eighteenth century slaves brought from Africa to exploit sugar cane.

The human face is made up of about 14 bones and there are about 43 muscles involved in the expression of more than 20 emotions.

Estephania Candelo is a physician, MSc in Genetics of Human Diseases and a tissue engineer from University College London. / Courtesy image

Today, the population of Cali is characterized by indigenous and mestizo communities, with components of Amerindian and African descent that predominate over the contribution of European descent.

In that population, Candelo and her team recruited 130 people who were divided into two groups: 79 made up what scientists call the control group; the rest (51) had a diagnosis of one of the following four syndromes: Down, Morquio, Noonan and neurofibromatosis type 1. All have one particularity: they cause alterations in the face (although some are more noticeable than others).

"We chose Down syndrome because it is one of the most common disorders; and Morquio syndrome because Colombia has one of the highest prevalences in the world. We included Noonan syndrome and neurofibromatosis type 1 because they are prevalent in Valle del Cauca and present more subtle altered craniofacial development", adds Candelo.

In order to measure the facial shape of each individual and detect the features associated with each disorder, the team took photographs. "We take 10 photographs at the same time and around the whole face, and with that we create a 3D mask of each face," explains Candelo.

To look even more closely, the scientists recorded the coordinates of a set of 18 landmarks around the lips, nose and eyes. They then compared the clinical evidence-based diagnosis with the Face2Gene diagnosis, and assessed the similarity between the Colombian patients and the 2D photos of the European patients.

The researchers were in for a surprise. Since Face2Gene launches a list of five diagnostic options after analyzing the person's face, the idea, if it is efficient, is that it will hit on the first option. This is what happened with Down syndrome. The artificial intelligence application confirmed this diagnosis in Colombian faces with this syndrome with 100% accuracy. But when it had to do it with the rest of the conditions, that percentage dropped.

When Face2Gene evaluated the faces of Colombian patients with neurofibromatosis type 1, it was only 8.3% accurate in that first diagnostic option. And the accuracy was 0 % with Morquio syndrome.

This result, the researchers write, suggests that, in a relatively common disorder on a global scale such as Down syndrome, where the algorithm is trained on the faces of thousands of individuals with a distinctive and well-represented facial phenotype, Face2Gene is efficient, regardless of the genetic or ancestry differences of the individuals; but that result is not the same when it comes to other rare disorders. "Because these types of algorithms are created in Europe and most of the photos they have been trained on have been European and North American, they can't recognize those differences. That is where the bias lies," explains the Cali native.

Adding more images of non-European faces into these types of applications could not only overcome that bias, but help science understand how the facial characteristics of these syndromes change according to ancestry.

Therefore, beyond evaluating the efficacy of Face2Gene, the team's research described the facial alterations of these disorders in the Colombian population. When comparing the local faces with the 2D images of Europeans, the researchers realized that although the application was effective in diagnosing Down syndrome, the mouths of the patients from Cali appeared wider than those of the Europeans.

This was not the only detail they picked up. In Noonan syndrome, scientists also reported changes related to the position of the mouth. Although these results are initial and could even be due to the patients' movements when taking the photos, for researchers they are strong enough to support the idea that rare disorders present specific facial features with characteristics that are significantly different in Africans, Asians and Latinos.

During the research, the team also looked at ears. "We noticed that our standard measurements did not include the ears. It turns out that most groups around the world working on facial morphology never include the shape of the ear. And maybe we're missing a key part of the story," Candelo says. Not to be left in doubt, they collected data and took photographs of that part of the face, recording the coordinates of eight landmarks.

After comparison, they found that the patterns of that part of the face were significantly different in Down and Morquio's syndromes from the control group. "We believe that the ears may have the potential to provide a new diagnostic approach to genetic diseases," says Candelo.

This finding earned the group recognition from the American Association of Anatomists, an international organization of biomedical researchers, which awarded the research a second place in the Postdoctoral Platform Presentation Award.

With all these clues, the way forward, says Candelo, is to know those features that differentiate European and non-European faces. "What for? To remove diagnostic barriers. Only about six out of 10 patients with rare diseases have an early diagnosis," answers Candelo.

An early diagnosis

As syndromes such as Down or Morquio syndromes have no cure, it is essential to diagnose them early. But this does not always happen because there is a difficulty in starting from a clinical suspicion of facial alterations: "There are few specialists who can think they are dealing with these syndromes", explains Ignacio Zarante, professor and researcher of Human Genetics at Universidad Javeriana. "Many times the diagnosis is discovered five, 10 or even 15 years late," adds the physician.

The problem with this delay is that, although these are incurable syndromes, science has advanced in therapies or treatments that can give some kind of management to the symptoms, processes that lose effectiveness as people grow older without the system recognizing their needs.

"But even in case of syndromes without any therapy, the diagnosis works for notification. No one can imagine the suffering of a person who goes to the doctor because they know or sense that something is wrong, and the doctor tells them that nothing is wrong. Living without a diagnosis is suffering," adds Zarante. A timely diagnosis is also essential for couples to be aware of the risks regarding possible future pregnancies.

"For all these reasons, we want to continue taking samples and feeding this algorithm in order to make it more effective with all faces," concludes Candelo. Ultimately, the aim is that the face of some of these syndromes is not just white and European.■