NEWS

# 'Founder effect' may have fueled fragile X cluster in Colombian town

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A semirural Colombian town called Ricaurte, about 150 miles southwest of Bogotá, may be home to the largest recorded genetic cluster of people with mutations linked to **fragile X syndrome**, according to a new study[1].

About 1 in every 19 men and 1 in every 46 women in Ricaurte have fragile X syndrome. Men there have 323 times the odds of having the condition compared with the general population, and women 192 times.

The cluster may be the result of a 'founder effect' from settlers who established the town in the late 1700s, the researchers say.

"It's a problem that originated from one of the founders who brought the mutation, and it expanded to other families," says lead investigator **Wilmar Saldarriaga-Gil**, professor of medical genetics at Universidad del Valle in Cali, Colombia. Some people in the town may be unaware of their mutation status before they have children, he says. (Saldarriaga-Gil spoke to *Spectrum* in Spanish, so we have translated his quotes.)

Fragile X is caused by mutations in the gene **FMR1**. The syndrome is associated with intellectual disability, physical abnormalities, seizures and, often, autism.

People with the syndrome have more than 200 repeats of the trinucleotide 'CGG' in a small section of FMR1. Those who have 55 to 200 repeats, or the 'premutation,' generally do not show features of the syndrome. However, they are at risk for a related condition called fragile X-associated tremor/ataxia syndrome; women in this category are also at risk for fragile X-associated primary ovarian insufficiency. The premutation can also develop into a full mutation over generations.

The researchers estimated that about 5 percent of the population of Ricaurte has either a premutation or a full mutation.

The town's residents have limited access to genetic counseling and basic health services, Saldarriaga-Gil says.

## Early clues:

When Saldarriaga-Gil was a young boy of about 6 years, his father occasionally took him to Ricaurte to attend church. He recalls noticing that many in the town were poor and were intellectually disabled.

In the late 1990s, after he completed medical school, Saldarriaga-Gil co-led a small study of Ricaurte residents. After identifying 19 people with fragile X, he decided to investigate the syndrome's prevalence in the town.

In 2015 and 2016, he and his colleagues went door to door to collect demographic data and blood samples from 926 people — nearly 80 percent of Ricaurte's inhabitants — aged 8 days to 96 years. They sent the samples to their collaborators at the University of California, Davis for DNA analysis.

The participation rate of "80 percent is very good," says **Eric Fombonne**, professor of psychiatry at Oregon Health & Science University, who was not involved in the study. However, families with a fragile X mutation may be more curious about the study and more likely to consent to participate compared with those who don't have a history of the mutation, he says. "That means that the prevalence [of the mutations] might be overestimated."

Of the 502 female participants, 11 have the full mutation and 20 have the premutation; and of the 424 male participants, 22 have a full mutation and 5 have a premutation. Another 22 women and 5 men have a 'gray zone' mutation — which comprises fewer CGG repeats than the premutation. The results were published 29 January in the *Journal of Medical Genetics.*

There's no reason to suspect that all of Colombia has a high prevalence of fragile X, but it's likely that towns near Ricaurte have elevated rates, Saldarriaga-Gil says.

## Founder effect:

Because most of the people with fragile X in Ricaurte are native to the town, their mutations may trace back to a common set of ancestors.

Ricaurte is thought to have been founded by 11 families, one from Spain and the rest from other parts of Colombia. The identified mutations may have originated in these families, Saldarriaga-Gil says.

To confirm this hunch, the researchers would have to sequence and analyze the residents' haplotypes, or DNA inherited across many generations.

"They didn't really do the ultimate experiment," says **Stephen Warren**, professor of human genetics at Emory University in Atlanta, who was not involved in the research.

Saldarriaga-Gil and his colleagues plan to do a haplotype analysis.

In the meantime, several Ricaurte residents with a premutation show signs of ovarian insufficiency, including early menopause, or of fragile X-associated tremor/ataxia syndrome, such as tremors.

Studying this population may provide insight into why only some people with the premutation develop these features.

"What you would wonder is whether there are other genes or perhaps environmental factors that could influence the development of the tremor/ataxia syndrome or that might influence the severity of the phenotypes with fragile X syndrome," says **Jim Grigsby**, professor of psychology and medicine at the University of Colorado in Denver, who was not involved in the research.

Ricaurte's large concentration of people with fragile X mutations may help answer these questions.

**REFERENCES:**

1. Saldarriaga W. *et al. J. Hum. Genet.* Epub ahead of print (2018) **PubMed**