

Cystic Fibrosis Research News

Title:

Extensive *CFTR* sequencing through NGS in Brazilian individuals with cystic fibrosis: unravelling regional discrepancies in the country

Lay Title: Extensive genetic testing in Brazilian individuals with cystic fibrosis: unravelling regional discrepancies

Authors:

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What was your research question?

Brazil is a continental country, and the Brazilian population has a wide range of ethnicities, due to migration waves mainly from Europe and Africa, together with native Indians. We suggested that Brazilians with CF from different Brazilian regions would have a specific distribution of *CFTR* variants (the gene affected in CF).

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Why is this important?

CF newborn screening (CF-NBS) started in 2000-2001 in three Brazilian states (Santa Catarina, Paraná and Minas Gerais), and theoretically, is currently available throughout the country, but is performed less efficiently in some regions. Access to CF treatment is also not equal across Brazil and seems to be affected by other health and social factors. Information on the genetic background of Brazilians with CF was scarce until recently and was based mainly on small mutation panels. These panels are tailored to detect *CFTR* variants common to North American or European populations and so not suited to the Brazilian population given its high degree of ethnic mixture.

What did you do?

We included individuals with CF in a genetic study if their data were available in the Patient Registry, but they did not have an established *CFTR* genotype (mutation). We used a modern and comprehensive strategy of sequencing the *CFTR* gene to identify the genotype and incorporated the results anonymously into the Registry Database. Genotyping results were expressed as 'positive', 'inconclusive' or 'negative'. We used statistical tests to investigate the link between the characteristics of the population/clinical information and the genotypes. We also ran an additional statistical test, (mediation analysis) to estimate the direct and indirect effects of the Brazilian region on the genotypes we found.

What did you find?

We were able to identify the genotype in a significantly higher proportion of people with CF, so that by October 2017, 3,104 (66.7%) of individuals had a genotyping result, as compared to only 46% in 2015. We identified a total of 236 *CFTR* variants (114 new variants), with F508del identified in 46% of the variants tested. Genotyping results classed 2,002 (64.5%) individuals as positive, 757 (24.4%) as inconclusive and 345 (11.1%) as negative. Distribution of genotype categories was markedly different across Brazilian Regions, with greater proportions of individuals classed as negative in the North (45%) and Northeast (26%) regions. CF-NBS and age at diagnosis were identified as mediators of the effect of Brazilian region on a positive genotyping result.

What does this mean and reasons for caution?

This marked difference of positive *CFTR* genotyping results among Brazilian regions may be related to a lack of reliable sweat testing resources, and a historically low provision of CF-NBS.



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The regions with the higher proportion of negative *CFTR* genotyping results are those with less access to CF-NBS and have the lowest values of the Human Development Index, which measures health, education and income in the country. This study reinforces the impact of CF-NBS in Brazil, which currently accounts for 60% of newly diagnosed cases. Among the limitations, the Registry includes historical data, and genetic data from these individuals may not be complete or accurate.

What's next?

A coordinated effort of healthcare providers and patients' associations must tackle these marked regional differences in Brazil, which are probably related to socio-economic conditions, lack of adequate CF-NBS and poor access to reliable sweat testing. These results may be useful to indicate regions where CF care demands more attention.

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