

## In psychiatric genetics, a push to think globally, act locally

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Credit : Susanna M. Hamilton, Broad Communications

Imagine you viewed the world's diversity solely through the lens of genetic and genomic data. Looking at the [gnomAD browser](#), for instance, you would think that more than 45 percent of humanity was

from Europe or had European ancestors. Data collected by the Psychiatric Genomics Consortium would leave you thinking all of us are either European (96 percent) or East Asian (four percent).

These numbers do not reflect reality. Fourteen percent of world is of African descent, 16 of European. Collectively, East and South Asia account for more than half of humanity. This disconnect skews our understanding of the full diversity of human genetics and how disease manifests in different populations.

"Most data on the genetics of human disease comes from northern European population registries and, increasingly, large U.S. health care systems," explained Steven Hyman, a Broad core institute member and director of the Stanley Center for Psychiatric Research at the Broad.

"But it is already clear from complex conditions like type 2 diabetes that studying populations with different genetic backgrounds can reveal really informative disease-associated alleles and genes.

"If genetics is the intellectual platform for understanding the biology of human illness," he added, "we need to incorporate as much human genetic diversity as possible."

The data diversity gap yawns particularly large for neuropsychiatric and neurodevelopmental disorders, contributing to disparities in therapies available for schizophrenia, bipolar disorder, autism, and other diagnoses around the world. This is particularly troubling given that neuropsychiatric conditions alone account for 25 percent of the global burden of disease.

"The data we have on psychiatric disorders are missing a massive amount of diversity. We're leaving out whole continents," said Karestan Koenen, a Broad associate member in the Stanley Center and a psychiatric epidemiologist at the Harvard T.H. Chan School of Public

Health. "And to put it bluntly, we're in danger of identifying therapeutic targets that may only be of use for white people."

For that reason, the Stanley Center and partners around the world have launched an ambitious effort to take psychiatric genetics global. Through an overarching effort called the Stanley Global Neuropsychiatric Genetics Initiative (a.k.a. Stanley Global), together they have created a set of massive-scale pilots aimed at vastly expanding the diversity of the genetic data available on psychiatric and neurodevelopmental disorders by collecting, sequencing, and analyzing samples from diverse populations around the world. One of Stanley Global's first major forays—a consortium dubbed Neuropsychiatric Genetics in African Populations (NeuroGAP)—recently started probing the genetics of schizophrenia and bipolar disorder in four nations across Africa.

What's more, Stanley Global has created a robust curriculum intended to foster independent, home-grown neuropsychiatric genetic research ecosystems, first in Africa and then beyond—making the tools and benefits of genetic science more broadly available around the world.

## **Capturing unseen diversity**

From a population genetics standpoint, Africa represents the greatest genetic diversity in the world, reflecting the human species' origins there. It stands to reason, then, that many traits and disorders should display greater genetic diversity compared to the rest of the world.

For psychiatric disease, however, little of that diversity has been captured. There have been few psychiatric genetics studies in Africa, with relatively small sample sizes. Even with other large genetics collaborations within Africa, such as the H3Africa Consortium, psychiatric disorders usually end up low on the priority list.

These factors raise the risk that psychiatric drug and diagnostic development could leave Africa behind.

"If we leave Africa out of psychiatric genetic research, the tools and drugs developed down the line may not be appropriate for patients there," said Koenen, who has a long-standing interest in working in Africa and who also studies the genetics of post-traumatic stress disorder. "A whole revolution in psychiatric genetics could bypass Africa."

NeuroGAP—a partnership helmed at the Broad by Koenen and spanning Ethiopia, Kenya, South Africa, and Uganda—aims to capture that diversity through what may be the largest collection effort yet mounted in Africa. The partnership's first study, called NeuroGAP-Psychosis, will collect saliva samples from more than 17,000 people diagnosed with schizophrenia or bipolar disorder, as well as an additional 17,000 people without these diagnoses.

It is a goal made possible through the efforts of researchers, clinicians, nurses, technicians, and project managers at more than 30 hospitals, clinics, and community health centers spread across the four participating countries.

"In previous studies that I've worked on in Africa, we've recruited 2,000 people at most," said Anne Stevenson, the program director for NeuroGAP-Psychosis. "To the best of my knowledge, nothing comparable has been done on this scale to date."

Each sample will be processed at its collection site, with DNA shipped to the Broad for DNA microarray genotyping and genome-wide association analysis. These analyses should identify unique genetic variations that correlate with participants' diagnoses.

"Even though we're not analyzing whole genomes," Koenen noted, "we should be able to retrieve tons of new information and help fine tune our understanding of what counts as a 'common' gene variant."

## **Laying strong foundations**

In developing their approach, the NeuroGAP-Psychosis collaborators have had to contend with the history of scientific inequity stemming from past interactions between western and African researchers.

"History has many examples of scientists from high-income countries who partner with African researchers, take samples and data, and are never heard from again," Hyman explained. "We want to avoid repeating those mistakes, and think about the kinds of infrastructure we can build and which will remain once this project is complete."

As a result, the NeuroGAP-Psychosis team has entered into truly collaborative partnerships with their colleagues in Africa, committing to share data openly (in keeping with the Stanley Center's dedication to open science), conduct analyses collaboratively, and work to foster a robust neurogenetic research enterprise within each participating country.

At the heart of this last commitment lies an innovative Stanley Global research training effort called GINGER (for Global Initiative for Neuropsychiatric Genetics Education in Research). Based at the Broad and the Harvard T.H. Chan School, GINGER comprises a two-year research education program with a critical purpose: to prepare a new generation of neuropsychiatric genetic researchers in Africa who will build on the discoveries of NeuroGAP-Psychosis and other projects (more on that in a moment) as well as chart new research avenues in their home countries.

"By promoting neuropsychiatric genetics research locally," Koenen explained, "we hope to help create a sustainable infrastructure through which psychiatric projects like this can be carried out and supported locally."

"And by raising the bar on the science," she continued, "we hope to draw more researchers into the field locally and bring more attention to these disorders."

"We want to train junior researchers and give them the tools to not just use data but build their own careers based on the data," added GINGER director, Broad associate member, and at Harvard T.H. Chan assistant professor Lori Chibnik. "By working together we build camaraderie that ultimately will lead to more intra-African collaborations, not just trans-Atlantic," she said. "We want to build research capacity by investing in people."

The GINGER team worked closely with the NeuroGAP site investigators to create an appropriate curriculum and train African researchers on a range of topics (e.g., informed consent, statistical analysis, population genetics). Their efforts have resulted in a comprehensive mix of mentoring, online coursework, and hands-on workshops in the U.S., Ethiopia, Kenya, Uganda, and the United Kingdom.

"The only way to ensure that a project's legacy lasts past its lifespan is to build the capacity of young and vibrant junior faculty to fill in the gaps and continue the work," said Dickens Akena, a psychiatrist and lecturer at Makerere University in Uganda and one of the NeuroGAP-Psychosis site leaders. "The GINGER fellowship was carefully crafted to identify promising faculty, train them according to local needs, mentor them, and help them grow over time."

"NeuroGAP represents an opportunity not only to contribute to the global body of genetic knowledge but also to build the capacity for research in our region and train our junior researchers to carry out their own studies," said Lukoye Atwoli, dean of Moi University School of Medicine in Kenya and another NeuroGAP-Psychosis site leader. "I expect that we will build capacity that can then help solve other health-related problems in our country."

"We've been involved in other projects where capacity building has been an element, but it's been a small part," added Dan Stein, head of psychiatry & mental health at the University of Cape Town and also a NeuroGAP-Psychosis site leader. "Here, building the next generation is key."

In addition to GINGER, Stanley Global has also established NeuroGenE, a major bioethics initiative created in collaboration with and led by neuroethicist Ilina Singh at the University of Oxford in the United Kingdom. Through a combination of bioethics research, practical ethics advice, training, and capacity building, NeuroGenE will support the Stanley Global projects, first in Africa and in the future other regions, by recognizing and collaboratively finding solutions for ethical questions and challenges that arise within and across scientific sites.

"Capacity-building in the ethics related to global neuropsychiatric research is core to the sustainability of this model," Singh explained. "Alongside the next generation of scientists, we need to build the next generation of neuroethicists."

## **A global approach**

NeuroGAP-Psychosis is not the only Stanley Global effort in Africa. Under development is a sister effort dubbed NeuroDev, that will focus on the genetics of neurodevelopmental disorders of childhood.



Neither is Stanley Global focused solely on Africa. The program is also building or conducting similar collaborative efforts with partners in:

- **China:** A schizophrenia project—led by institute members Benjamin Neale and Mark Daly and Stanley Center Asia Initiatives director Hailiang Huang—plans to sample five ethnic populations across six provinces and regions, in collaboration with BioX-Shanghai Jiao Tong University and Xi'an Jiaotong University.
- **Finland:** In collaboration with Finland's Institute for Molecular Medicine, National Institute for Health and Welfare, and Social Insurance Institution, and Finnish university hospitals, this collaborative project, led by associate member Aarno Palotie, will study the genes of 10,000 schizophrenia patients. (The people of Finland have a genetic background unique among European populations.)
- **Mexico:** A collaborative project with Mexico's National Institute of Psychiatry, overseen at the Broad by Koenen, aims to collect samples from 4,000 people diagnosed with psychosis and 4,000 controls from Mexico City and Campeche.

Hyman believes fully that the the time to undertake these efforts is right now, especially if we are to capture the energy around genetics and global health.

"We're in the age of human genetics and genomics, and people around the world are geared up to find new knowledge and put it to use in understanding and addressing human disease," Hyman said. "If we delay seriously studying diverse genomes, in essence we delay all of biology, and projects that could benefit millions in the developing world will just fall off the map. We need to move ahead as rapidly and effectively as we can."



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