An Analysis for Anxiety

An integrative approach to translational research is providing new insights into the molecular mechanisms of psychiatric disorders.

Compared to other major psychiatric disorders like depression, schizophrenia, or bipolar disorder, generalized anxiety disorder — a category under which many anxiety-related disorders fall — is relatively understudied from a genomic standpoint.

The prevalence of these disorders, combined with the dearth of genomic data for them, led Indiana University School of Medicine's Alexander Niculescu to use an integrative, translational research approach to study anxiety disorders, with an eye toward developing personalized treatments.

In an April 2011 Translational Psychiatry *paper, Niculescu and his colleagues describe how they identified several candidate genes, blood-brain biomarkers, and possible mechanisms for anxiety disorder. Niculescu and his team found notable genetic overlap between anxiety and schizophrenia. That the two appear to be somewhat genetically interdependent led Niculescu's team to propose "schizo-anxiety" as a new diagnostic domain.* Genome Technology's *Matthew Dublin spoke with Niculescu about the study. What follows is an excerpt of their conversation, edited for space.*

GENOME TECHNOLOGY: What was your strategy for mapping the genomic landscape of anxiety disorders?

ALEXANDER NICULESCU: We used an approach that we developed over the last decade called "convergent functional genomics." This is essentially like a Google page-rank algorithm wherein the more lines of evidence converge on a gene or biomarker, the higher it comes up on your prioritization list. The lines of evidence that we're using are in our own experimental data — primarily gene expression and animal models — but also integrated with our own gene expression and genetic data from human studies and the existing literature. In a nutshell, we did some animal model experiments with gene expression studies in the brain and blood of those mice, we prioritized those genes using the convergent functional genomics approach, and we did higher-order analysis looking at biological mechanisms and pathways involved.


ALEXANDER NICULESCU

GT: How is your research geared toward the treatment of anxiety-related disorders?

AN: Our work has always been about taking things to the clinic. We have a lot of work in the lab where we look at human blood gene expression studies as a way of finding blood biomarkers and developing blood tests for psychiatric disorders, so we have an active research line in mood disorders and psychotic disorders and so on. This foray into anxiety ... we're trying to do what we did for bipolar disorder and schizophrenia, where we developed proto-type blood biomarker tests that could have clinical applications. We identified some very interesting candidate biomarkers that are co-directionally changed in blood and in the brain. … The next step is to validate these biomarkers in human studies, and that's what we're doing now.

GT: How have advances in genomics and sequencing technology affected psychiatry?

AN: We are about five to 10 years behind where cancer is right now for two reasons: Our phenotype is more complex than cancer because psychiatric disorders are more complex and less well-defined, and [limited] accessibility of tissue that allows you to do all this gene expression stuff. Whereas most cancers are amenable to biopsies, you can't biopsy a live brain. I think the recent revolution in our area is that you can actually profile peripheral tissues — whether blood, or induced pluripotent stem cells, or olfactory cells — and get a gene expression signature readout that's informative and correlates with some of the things that occur in the central nervous system. So I believe that will permit us to catch up with the advances that have already occurred in cancer.

GT: Do you foresee changes to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* categorization of

diseases from the continued application of your approach to the study of other psychiatric disorders?

AN: Our emerging appreciation of the complexity, heterogeneity, overlap, and interdependence of major psychiatric disorders as currently defined and their biological building blocks/Lego-like nature, may make the development of tests for specific modular or dimensional disease manifestations — such as mood, psychosis, anxiety — more useful and precise than those for broad diagnostic categories like schizophrenia, bipolar disorder, or post-traumatic stress disorder. The DSM may function as a living and evolving document, with more frequent upgrades and updates than in the past.

GT: How close are mental-health care providers to offering personalized treatment for psychiatric disorders?

AN: It will [be] five years from now, because a lot of the tools and the know-how are already here — they just have to be standardized and integrated in a systematic fashion into clinical practice. We might see in three to five years some of these things directly contributing to day-to-day care. The driver for this will be not just patients who will get involved and demand this stuff, but because personalized, genomic psychiatric care will also reduce costs in the long run, large payors involved will want to have this more precise approach because it will save on hospitalizations and health-care costs. So there's going to be pressure from a lot of sides to move this stuff along fast.

GT: How will the $1,000 genome affect psychiatry, and benefit patients with anxiety related disorders?

AN: I don't think that sequencing technology is really going to be the bottleneck for us. The technology is not the problem — it's becoming more higher-throughput every year and generating more data. The problem really is the analysis. The $1,000 genome is fine, but it's going to be a $1 million analysis, so that's where we're focusing our efforts. It's also an issue of genetic heterogeneity — patients are very diverse, and really profiling patients and understanding what each patient has and treating them in a personalized fashion is where we're trying to move. All these high-throughput tools for sequencing and gene expression are very important for being able to treat patients as individuals, but the data analysis is the key factor in terms of making sense of all that information. ■