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New hope in the pipeline for autistic individuals

29 April 2019 | Features | By Manbeena Chawla

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Autism is a lifelong disorder without many treatment options that often leads to patients requiring constant care and increased responsibilities for their family members. In the recent years, several drug discovery initiatives have been launched, informed by work of basic neuroscience, that seek to change how the autistic brain functions and responds. But almost all of these drugs have faced serious hurdles in clinical trials. Why? Because apart from behavioral psychoanalytical tests, there exist very few ways to measure whether a person responded to the drug. It's even less possible to predict whether a person will have side effects or not. These, in technical terms are called diagnostic biomarkers.

Diagnostic biomarkers, simply put, are a molecular bar code to predict differences in patients and their treatment outcomes. Such a barcode is being developed for a specific form condition called Fragile X syndrome (FXS) that is the leading inherited cause of autism worldwide. These findings were reported in a new paper in Nature Communications. In a joint collaboration, between research groups at Center for Neural Science, New York University and Centre for Brain Development and Repair in InStem, Bangalore; three main scientists, Heather Bowling and Eric Klann (NYU) and Aditi Bhattacharya (inStem) have identified proteins that are differently made in FXS by using mice models and human plasma from FXS patients which can serve as future diagnostic markers.

Conservative estimates report that FXS affects approximately 1 in 2500-4000 males and 1 in 7000-8000 females. The number of female carriers are as high as 1 in 130-250 population, whereas male carriers status are 1 in 250-800 population. These incidence rates are not specific to any geographic region making the syndrome a 'world' problem. Although it has been more than 25 years since the gene for FXS was discovered and many basic disease mechanisms are known, there is no approved medication available for this condition. Numerous drug trials for FXS were conducted between 2007 -- 2014, but they failed to meet to the main criteria set for treatment effectiveness.

Recent work carried out in the last 10 years or so have shown that FXS model mice have 'eccentric' protein synthesis, meaning that there are a large number of proteins that are either are made too much or made too little."Improper production of new proteins is the heart of the problem in FXS," says Aditi. It is well known that proteins are the most critical executors of brain function and changes in the way they are made can have profound and lasting consequences. She says, "Previous animal studies have shown a correlation of improvement in behavioral measures modeling human symptoms with corrected protein synthesis in models of FXS. However, what proteins are synthesized inappropriately in FXS brains that cause neurons to malfunction is not clear."

Mapping the proteins that are made differently in FXS could lead to a method (or “biomarker”) to test whether a drug is efficacious by restoring the normal levels of these proteins and to identify subpopulations of patients who may respond differently. Aditi and her colleagues measured newly synthesized proteins in the brains of FXS model mice at rest and in response to neuronal activity. Using a multi-step statistical and confirmation paradigm, they identified a large number of proteins previously unknown in FXS pathology.

It is likely that proteins that are improperly regulated in the brain may also be regulated improperly in tissues like blood that are more accessible, so they determined whether altered protein levels observed in the brain also were observed in blood. When they compared the blood of patients with FXS to healthy volunteers, they found that many of the proteins either differed entirely between patients and healthy volunteers or they differed in some patients and not others.

Finally, they tested in mice, whether the experimental drugs (from clinical trials) could change levels of the blood proteins and found that that was indeed the case and the response differed for each drug.
“In this paper we present the beginnings of a molecular bar code for cataloging patient sub-groups and predicting which patient will respond better with what drug and whether the drug is doing its work in the body or not," concludes Aditi.

Professor Flora Tassone is a FXS researcher at the UC Davis School of Medicine. She said that, “To date, there is no cure or approved medication for the treatment of the underlying causes of FXS. In addition, there are no biomarkers, and in particular, blood-based biomarkers, which are essential for objectively monitoring and assessing disease severity, for predicting efficacy of response to drug treatment and for defining subgroups of responders in FXS.”

She felt that “this issue has become particularly important in the past years as multiple targeted drug treatments have failed on their primary endpoints and several more drugs are currently in various stages of clinical development. These outcomes have highlighted the urgent need for the development of biomarkers able to evaluate the clinical benefit of pharmaceutical interventions. This collaborative work is of relevance as it identified altered expression of a number of proteins which are potential candidate biomarkers that respond to treatment in the mouse model of FXS. Importantly, their further investigation led to the observed differences in blood expression of these proteins between patients with FXS and non-FXS healthy controls suggesting that they could be utilized as molecular biomarkers in individuals with FXS.” Dr. Tassone feels understanding how a single-gene dysregulation in FXS affects genetic and neural network processes will help to develop targeted treatment in other neurodevelopmental disorders such as ASD due to their neurobehavioral similarities.

“We have many biosamples from previous human trials to test next and they could actually tell the exact effects as well as side effects that the drugs may have on the individuals with FXS,” says Aditi. Aditi and Eric’s groups are open to commercial development, and their next step in the research will involve conducting human trials in large numbers so that the molecular bar code can be thoroughly tested and used to help future drug development trials for FXS and autism.