

Researchers explore new method for early disease diagnosis



From left, Purdue University assistant research scientist Nagana Gowda and chemistry professor Daniel Raftery discuss their work with Murthy Shanaiah, a post-doctoral research assistant, and graduate student Aruni DeSilva who is seated in front of the tank. The researchers are performing an analysis, using nuclear magnetic resonance spectroscopy equipment. Raftery's team established a new technique for detecting a number of genetic disorders found in infants and young children. Credit: Purdue News Service photo/David Umberger

Purdue University researchers worked with the Indiana University School of Medicine to establish a technique that provides a new approach for detecting a number of genetic disorders found in infants and young children.

Daniel Raftery, a Purdue professor of analytical and physical chemistry, and his collaborators used a simple chemical reaction to improve the ability to detect important molecules in complex fluids like blood and urine. The technique makes the markers for some genetically caused metabolic disorders up to 100 times more visible, Raftery said.

"This technique allows us to profile a class of biomarkers - molecules that indicate disease - that would otherwise be very difficult to detect," he said. "The increased sensitivity could allow doctors to diagnose a range of diseases at very early stages. We examined genetically based metabolic disorders, or inborn errors of metabolism, because it is especially important that they be treated early in a child's life in order to prevent tragic effects such as brain damage. The technique also could catch borderline cases that may have otherwise gone undiagnosed until serious symptoms arose."

Bryan Hainline, director of the clinical division of the Department of Medical and Molecular Genetics and clinical associate professor in the metabolism division of the Department of Pediatrics at Indiana University School of Medicine, provided access to clinical samples and insight into the markers of metabolic disorders. The IU team was critical to the success of this work, Raftery said.

"The combination of Purdue's research strength in chemistry and the IU School of Medicine team's knowledge of pediatric metabolic disorders allowed us to quickly advance this technology," he said. "We were able to evaluate the accuracy of the technique by testing it on samples known to contain certain concentrations of various markers."

This method of analysis, called metabolomics, involves the simultaneous analysis of multiple small molecules, or metabolites, which occur in fluids and tissues in the body. The presence of a particular metabolite, grouping of metabolites or ratio of metabolites can indicate a response to biological stress or a specific disease state.

"The metabolic profile in biofluids, such as blood and urine, provides a snapshot of ongoing biological processes in the human body," Raftery said. "This type of analysis could be a key to earlier detection of

diseases. Metabolic analysis is currently being developed to identify diseases such as cancer and cardiovascular disease. However, we need to continue to work to refine and improve the techniques to provide early detection."

Raftery and his team used nuclear magnetic resonance spectroscopy, a cousin of magnetic resonance imaging, which provides a reproducible and quantitative measure that provides the broadest spectrum of molecules for metabolite profiling. The spectrum is represented by a pattern of peaks corresponding to different frequencies that can be used to identify the molecules like amino acids in biofluids. Each metabolite has a unique pattern of peaks.

Researchers use nuclear magnetic resonance to detect hydrogen or carbon atoms to provide insight into the metabolites present, however this standard approach has disadvantages, Raftery said. The signals from carbon atoms are very weak and are difficult to detect, while the signals from hydrogen atoms often overlap. In particular, metabolites present in high concentrations overlap those present in low concentrations.

Raftery and his team enhanced the visibility of a certain type of metabolites, amino acids, by chemically tagging the molecules of interest so that they are more easily visible.

"We added a chemical that reacts with the amino acids and similar metabolites and forms a tag that can be seen through nuclear magnetic resonance," he said. "The tag actually is an easily identifiable isotope, in this case a carbon atom that is heavier than the standard carbon atom. Because we can easily detect this isotope, it causes these tagged metabolites to effectively pop out against the background of all of the others."

In addition to Raftery and Hainline, Narasimhamurthy Shanaiah, M. Aruni Desilva, G. A. Nagana Gowda and Michael A. Raftery, all from Purdue's Department of Chemistry, co-authored a paper detailing this research that was published in the July 10 issue of the *Proceedings of the National Academy of Sciences*.

In addition to its increased sensitivity, the new testing method requires little pretreatment of the sample and roughly 0.5 milliliters of blood to perform the test. The entire test can be performed in about half an hour, providing a quick turnaround for results and treatment decisions for patients, Raftery said.

"It is a very simple process and would not require much training to perform the tests," he said. "It is an easily reproducible test that can be done over and over again, which is important to ensure accurate diagnosis."

Raftery said he plans to continue to work with the IU School of Medicine to perform additional tests on clinical samples, to look at more samples from borderline cases and to examine other diseases.

"This approach is applicable to a variety of molecule types and other fluids, and has the potential for additional applications," Raftery said. "We plan to test more samples and to determine if this methodology proves to be sensitive to cancer and heart disease, as it is for metabolic disorders. We also plan to try other sample types such as tissue."

Source: Purdue University

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