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Discovery of new type of RNA could have implications for some congenital disorders

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State funding of stem cell research at the UConn Health Center has led one research team to the discovery of a new type of RNA that could one day result in the successful treatment of devastating congenital disorders such as Prader-Willi syndrome.

Gordon Carmichael, professor in the Department of Genetics and Developmental Biology, together with his former Ph.D. student Ling-Ling Chen, who is now a professor, along with her students in Shanghai, used stem cells to look through the entire human genome to search for new molecules. "We found RNAs that no one had ever found before," Carmichael says. "We found it using a unique mechanism that we had discovered. This RNA was missed because it didn't have the typical identifiers of other types of RNA."

The newly discovered sno-IncRNAs, described in an article published in the Oct. 26, 2012 issue of *Molecular Cell*, is located in a region of the human genome that is not expressed in patients with Prader-Willi syndrome (PWS) and Angelman syndrome (AS). "Every Prader-Willi patient in the world fails to express these RNAs," Carmichael explains. "We went on with our study and found out how we think they are working."

In a lab virtually next door to Carmichael's are researchers Marc Lalande and Stormy Chamberlain, whose team used state stem cell funds to create genetic models of PWS and AS. "We just stumbled on this discovery," Carmichael says of his work, "and it just so happens that two

of the world's experts on these diseases are flanking us. It's now leading to collaborations between our labs and major new molecular insight."

"The goal of stem cell research is to improve human health, and at UConn we have a large portfolio of stem cell research projects," says Lalande, professor and chairman of Genetics and Developmental Biology. "Our labs have generated stem cells from the skin of Prader-Willi and Angelman patients. The new class of RNA discovered by Gordon Carmichael has significant importance in these two syndromes. So two very separate projects funded by the state initially, and now federally, have crossed paths and intersected to advance our knowledge of a complex human genetic disorder. That's remarkable."

The state committed to a 10-year, $100 million investment in stem cell research starting in 2006. The early results from that research jump-started funding from federal grants and other sources. The goal of the state's investment is to move Connecticut toward becoming a national and world leader in stem cell research. This in turn could have huge economic benefits, such as start-up companies, as scientists learn how to repair or replace damaged or missing genetic molecules to treat a wide variety of diseases.

Carmichael, whose research initially had focused on mouse viruses, moved to stem cells when he received one of the first state grants. "Stem cell grants have changed my world," he says. "This type of funding has changed how I do science. Now my expertise is in studying the underlying mechanism of disease." His research has resulted in more than a dozen major papers published worldwide, and grants flowing into the Health Center at a time of stiff competition for funds.

Prader-Willi syndrome is a congenital disease caused by missing paternal genes on part of chromosome 15. These genetic changes occur randomly; patients usually do not have a family history of the condition.

Signs of PWS at birth include poor weight gain and failure to grow and thrive in early infancy. As PWS children grow, this reverses itself. In addition to having intellectual and behavioral disabilities, they develop an intense craving for food, often resulting in morbid obesity. These symptoms can in turn lead to diabetes and other serious health problems.

Angelman syndrome is a genetic disorder that involves the same part of chromosome 15 as PWS and results from the lack of a functional copy of the UBE3A gene inherited from the mother. Infants often have feeding problems from birth and developmental delays by 12 months. Seizures usually begin between ages 2 and 3. Children will experience impaired speech, motor difficulties, hyperactivity, and balance and sleep disorders that continue into adulthood.

Research into these related disorders is encouraged and funded by the Foundation for Prader-Willi Syndrome, says Theresa Strong, chairwoman of the Foundation's scientific advisory board. "Because Prader-Willi is a rare disorder, patient advocacy groups are important in promoting research. Mouse models do not recapitulate disease very well. Stem cells allow the scientific community to study this disease in a way that they have never been able to study it before."

As the parent of an 18-year-old son with PWS, Strong says she yearns for an effective treatment, of which there currently are few. Most families live with locks on their cabinets and refrigerator. The chronic hunger of PWS patients lasts a lifetime.

"Failure to thrive when children are very young is replaced by an insatiable appetite," she says. "They are constantly hungry but don't need that many calories. It's a nightmare scenario where you have to restrict their environment, because food is all around us. They can't be independent because they can't control their appetite. It's a source of frustration all around."

Research into PWS could lead to life-changing results, says Strong, who is a scientist herself. "If not for the hunger issue, there's a lot that many of these kids could do. We could make a significant impact in their lives and their ability to contribute to society."

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