Researchers iron out new role for serotonin

January 27 2009

Vanderbilt University Medical Center investigators have found a surprising link between brain iron levels and serotonin, a neurotransmitter involved in neuropsychiatric conditions ranging from autism to major depression.

Appearing in the *Proceedings of the National Academy of Sciences* this week, the study by Randy Blakely, Ph.D., and colleagues also demonstrates the utility of a powerful in silico approach for discovering novel traits linked to subtle genetic variation.

The serotonin transporter protein (SERT) regulates serotonin availability in the brain and periphery, and variations in human SERT have been linked to many neurobehavioral disorders - including alcoholism, depression, autism and obsessive-compulsive disorder. SERT is also a major target for medications like the selective serotonin reuptake inhibitors (SSRI) used for treating depression.

Thanks to a serendipitous mix-up in an animal order, Blakely and first author Ana Carnerio, Ph.D., discovered that a mouse strain they had been using to studying SERT function - called C57BL/6 - actually carries a mutation that reduces the function of the transporter.

"Importantly, low-functioning variants of human SERT have been associated with anxiety, depression, and reduced efficacy of SSRI medications," notes Blakely, senior author and director of the Vanderbilt Center for Molecular Neuroscience.

By querying an online resource called the Mouse Phenome Database, they found that most mouse strains possess a SERT version called "ER" - which is identical to the sequence found in human SERT. A small number of strains, however, including the commonly studied C57BL/6 strain, carry a different version (called "GK").

Carneiro realized that she could utilize her identification of SERT GK to elucidate new aspects of brain chemistry and behavior. Vanderbilt collaborator David Airey, Ph.D., helped Carneiro and Blakely exploit a separate panel of mice where the SERT GK variant is presented on many different genetic backgrounds - a so-called "recombinant inbred" population termed BXD mice.

Using lines from this population, the team found that SERT GK mice performed differently than SERT ER mice on tests of anxiety and depression, consistent with reduced function of SERT GK. Importantly, a public database of anatomical, biochemical and behavioral features exists for all mice in the BXD population, allowing Blakely and colleagues to identify novel traits linked with the low functioning SERT. From this in silico approach, Blakely and colleagues identified multiple trait differences affected by the SERT GK/ER variation, including traits associated with alcohol consumption and brain dopamine signaling.

Additionally, they found that iron levels in the brains of mice with the GK variant were significantly higher than in the ER variant mice. Iron is required to synthesize both serotonin and dopamine, and serotonin receptors are known to regulate iron-carrying proteins. But SERT had not been previously shown to control brain iron levels. Follow-up studies with mice where the SERT gene was eliminated (SERT "knock-out" mice) verified a critical role for the transporter in controlling brain iron levels.

"Because SERT is such an important drug target in treating anxiety,

depression and OCD, we need to stop and think about how iron might be influencing these disorders," Blakely said. The study also demonstrates the power of an in silico approach - combined with traditional experimentation - in understanding how genes affect complex traits.

"The broader number of findings in our paper derives not from (experiments) we did, but from what the (scientific) community collectively did to populate the BXD database," Blakely noted.

"Indeed, this is a great example of how biostatistical approaches can help limit the amount of experimentation that is needed with animals."

Source: Vanderbilt University