Understanding and treating the cognitive dysfunction of Down syndrome and Alzheimer's disease

March 1 2012

Down syndrome (DS) is the most common genetic disorder in live born children arising as a consequence of a chromosomal abnormality. It occurs as a result of having three copies of chromosome 21, instead of the usual two. It causes substantial physical and behavioral abnormalities, including life-long cognitive dysfunction that can range from mild to severe but which further deteriorates as individuals with DS age.

It is not currently possible to effectively treat the cognitive impairments associated with DS. However, these deficits are an increasing focus of research. In this issue of Biological Psychiatry, researchers at Stanford University, led by Dr. Ahmad Salehi, have published a review which highlights potential strategies for the treatment of these cognitive deficits.

The authors focus on insights emerging from animal models of Down syndrome and outline the structural abnormalities in the DS brain. They also discuss studies that have linked the overexpression of the amyloid precursor protein gene, called APP, to the degeneration of neurons in mice. These findings have led to the development of therapeutic treatments in mice, which now must be tested in humans.

"For more than a decade, we have been working on identifying a strategy to treat cognitive disabilities in our Down syndrome mouse models," said Dr. Salehi. "Considering the research and results with mouse models as

an indication of success of a strategy in humans, we are ever closer to finding ways to at least partially restore cognitive function in children and adults with Down syndrome."

Interestingly, this research is also providing insights into Alzheimer's disease (AD), the archetypal disorder of late life. All adults with Down syndrome develop AD pathology by age 40, and there are some remarkable similarities in the brain degeneration and cognitive dysfunction of individuals with DS and those with AD.

The leading AD hypothesis posits that it is caused by increasingly elevated levels of amyloid-related proteins, which are toxic to nerve cells in the brain. These same proteins also accumulate in the brains of people with DS because they are made by the APP gene, which is located on chromosome 21. Individuals with AD don't have the extra chromosome, of course; rather, it is mutations in APP that appear to cause the brain degeneration associated with AD.

Dr. John Krystal, editor of *Biological Psychiatry*, commented: "The convergence of research on Down syndrome and Alzheimer's disease highlights a central point that cannot be overstated. When we understand the fundamental biology of the brain, important new conceptual bridges emerge that guide new treatment approaches."

Salehi added, "In the near future, we may very likely look back with the perspective that Down syndrome represents an example of how families of affected individuals came together and by supporting basic research, changed the course of a disorder that was considered untreatable for more than a century."

More information: The article is "Neurobiological Elements of Cognitive Dysfunction in Down Syndrome: Exploring the Role of APP" by Martha Millan Sanchez, Sietske N. Heyn, Devsmita Das, Sarah

Moghadam, Kara J. Martin, and Ahmad Salehi (doi:10.1016/j.biopsych.2011.08.016). The article appears in *Biological Psychiatry*, Volume 71, Issue 5 (March 1, 2012)