'Brain-only' mutation causes epileptic brain size disorder

April 11 2012

Scientists have discovered a mutation limited to brain tissue that causes hemimegalencephaly (HMG), a condition where one half of the brain is enlarged and dysfunctional, leading to intellectual disability and severe epilepsy. The research, published by Cell Press in the April 12 issue of *Neuron*, has broad significance as a potential model for other complex neuropsychiatric diseases that may also be caused by "brain-only" mutations.

Mutations can be inherited or occur spontaneously. Inherited mutations are present throughout all cells of the body, but some spontaneous mutations can occur during development and hence be limited to cells in some organs but not others. For some time it has been suspected that there might be neurological diseases that are caused by mutations limited to the brain, but this had not yet been definitively demonstrated as it is very difficult to study brain tissue.

"The striking asymmetry of the brain in individuals with HMG has long suggested that this disease may be caused by a spontaneous mutation restricted to one half of the brain and detectable by direct study of affected brain tissue," explains the study's first author, Dr. Ann Poduri, from Children's Hospital and Harvard Medical School.

Patients with HMG often have dozens of seizures per day, which so interferes with their cognitive development that doctors make the difficult decision to remove brain tissue in a desperate attempt to control the seizures. Fortunately, these operations are frequently successful in

controlling seizures and allowing children to develop remarkably normally. Such operations provided brain tissue samples that were used by Dr. Poduri and her colleagues to identify mutations in the AKT3 gene in HMG brain tissue. Previous research has linked AKT3 with the control of brain size. The AKT3 mutations were restricted to the affected brain tissue, and were not evident in blood cells, suggesting that the mutation was spontaneous and not inherited.

"Our data suggest that spontaneous mutations resulting in abnormal activation of AKT3 contribute to overgrowth of one-half of the brain. The size and architecture of HMG may be determined in part by the stage at which the mutation occurs relative to the stage of brain development," concludes senior study author, Dr. Christopher Walsh from Children's Hospital Boston, Howard Hughes Medical Institute, and Harvard Medical School. "It is also notable that, to our knowledge, this is the first disease attributed to mutations that are limited to brain tissue. There are other epilepsies and neuropsychiatric diseases that are associated with spontaneous mutations and are therefore also candidates for these sorts of 'brain-only' mutations."

The study was supported by the Howard Hughes Medical Institute, the National Institute of Neurological Diseases and Stroke, and the National Institute of Mental Health.

More information: Poduri et al.: “Somatic Activation of AKT3 Causes Hemispheric Developmental Brain Malformations.” DOI:10.1016/j.neuron.2012.03.010

Provided by Cell Press