

JULY 24, 2008

## Eye Movement Disorder Caused by Improper Development of Motor Neurons

An international team of researchers has identified a gene mutated in Duane syndrome, a common disorder that restricts the movement of the eyes.

The research group, led by Howard Hughes Medical Institute (HHMI) investigator Elizabeth C. Engle, published its article on July 24, 2008 in *Science Express*, which provides electronic publication of selected *Science* papers in advance of print. The new research confirms and expands on the Engle lab's longstanding hypothesis that many congenital complex eye movement disorders arise from improper development of the nerves that control movement of the eyeball. Researchers once thought the disorders resulted from muscle defects.

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— Elizabeth C. Engle

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Duane syndrome, with an incidence of 1 in 1,000 people, is the most common congenital complex eye movement disorder. Affected individuals, cared for routinely by ophthalmologists throughout the world, are unable to move their eye(s) in a particular direction: People born with this condition cannot move one or both eyes outward toward their ear, said Engle, who is at Children's Hospital Boston and Harvard Medical School. When they try to look out, the eye doesn't move. When they look in, the eyeball retracts and gets pulled back into the socket.

The team studied the only inherited form of Duane syndrome identified in large families. In earlier linkage analysis studies, researchers identified a region, or locus, on chromosome 2 that held the genetic mutation unique to the affected family members. The large-scale project reported in *Science* benefited from collaborations with the researchers who had previously genetically mapped the disorder using linkage analysis and with clinicians

worldwide who identified additional families with Duane syndrome, said Engle. Additionally, neurodevelopmental biologists, including Professor Sarah Guthrie at King's College in London, modeled the genetic defect in chick embryos.

Engle's team zeroed in on the Duane syndrome gene by studying DNA extracted from blood or saliva samples provided by multiple members of different families that mapped to the locus that was identified in the genetic linkage studies. By screening genes in the linked region, Engle's group identified a unique mutation in the gene *CHN1* in each of seven families. *CHN1* encodes a RacGAP signaling molecule,  $\alpha$ 2-chimaerin, which previous studies in mice had shown to be essential for normal upper motor neuron axon guidance.

In contrast, Engle and her colleagues found that the Duane syndrome mutations led to the over-activity of  $\alpha$ 2-chimaerin in humans. That overactivation of  $\alpha$ 2-chimaerin resulted in a lower motor neuron defect. Engle and her colleagues next recreated the mutation in developing chick embryos. In the chick, the team saw that the developing nerve stalls out and doesn't make it to its target muscle. Engle hypothesizes that this happens because the *CHN1* mutation increases the activity of the  $\alpha$ 2-chimaerin protein, blocking the ability of the nerve to respond to growth signals that normally target the nerve to the muscle.

These human mutations, said Engle, likely disconnect the response of the nerve to growth signals, so the nerve doesn't appropriately reach the muscle. The new research illustrates at the molecular level how neuronal wiring can go wrong in early development to cause Duane syndrome. This is a nice example of an error in the development of a very simple motor circuit, she continued. If we can understand the wiring of these simple circuits, we may be able to better understand wiring of more complex neural circuits as well.

In the longer term, Engle added, the work may also lead to a better understanding of the fine-tuning of RacGAP signaling molecules necessary for the development of motor neuron circuits: It is intriguing that loss-of-function studies revealed the necessity of  $\alpha$ 2-chimaerin for correct upper motor neuron wiring, she said, while our work now demonstrates that over-activity of  $\alpha$ 2-chimaerin disrupts human lower motor neuron development. Future functional studies should provide insight into the fine-tuning of  $\alpha$ 2-chimaerin and other RacGAP signaling molecules in neural development.

Vision requires rapid, precise, and coordinated eye movements, Engle said, and we continue to find that congenital eye movement disorders are a very sensitive indicator for errors in the development of motor circuitry.