Scientists uncover evolutionary keys to common birth disorders

January 14 2009

The work of Forsyth scientist Peter Jezewski, DDS, Ph.D., has revealed that duplication and diversification of protein regions ('modules') within ancient master control genes is key to the understanding of certain birth disorders. Tracing the history of these changes within the proteins coded by the Msx gene family over the past 600 million years has also provided additional evidence for the ancient origin of the human mouth.

Dr. Jezewski has published an important study examining the Msx family that has ancient roots as a master control gene for patterned embryonic growth. Previous work by Dr. Jezewski, and other groups, identified mutations within the human MSX1 gene in two different birth disorders: either cleft lip and palate or skin derivative disorders ('ectodermal dysplasias') that include tooth and nail malformations. The mutations associated with the more severe clefting disorder are found within unique portions of the MSX protein, thus providing the first molecular explanation for this disease pattern. This work may eventually enable genetically susceptible families with environmental risk factors to prevent these common birth disorders.

Cleft lip and palate is one of the most common birth defects. Both genes and environment contribute to this condition. "If we can learn more about genetic susceptibility of these families, we can start to examine how environmental factors, like maternal smoking, may contribute to their manifestation," says Dr. Jezewski. "This information could lead to recommendations for appropriate behavioral changes within families who are genetically at risk."

Summary of Study

The study, "Domain duplication, divergence, and loss events in vertebrate Msx paralogs reveal phylogenomically informed disease markers," was published in *BMC Evolutionary Biology* January 14, 2009. This research was led by Dr. Peter Jezewski at The Forsyth Institute, and was conducted with collaborators at Boston University, Drs. John Finnerty and Maureen Mazza. The research team performed a battery of evolutionary analyses on 46 Msx proteins from a diverse collection of animals, ranging from sponges to humans. This analysis identified human sequence variants in Msx likely to underlie disease, and indicated why mutations in the same gene can lead to either orofacial clefting or ectodermal dysplasias.

These clinical insights were gleaned from work demonstrating that certain portions of the Msx proteins have remained constant over extremely long periods of time (>600 million years) while other Msx protein modules had duplicated and then subsequently diverged within the duplicated Msx sister genes, a previously unrecognized avenue for the evolution of morphological innovation. These observations will help to prioritize future clinical and functional research on these disease mutations. An outgrowth of these insights was the realization that the highly conserved protein modules that make up the Msx protein help to define a class of animal specific master control genes that each go on to specifically pattern the body plan of all modern animals.

Source: Forsyth Institute