Modeling Human Craniofacial Birth Defects with ORNL Mouse Mutations

Mouse Genetics and Functional Genomics Program – June 2002

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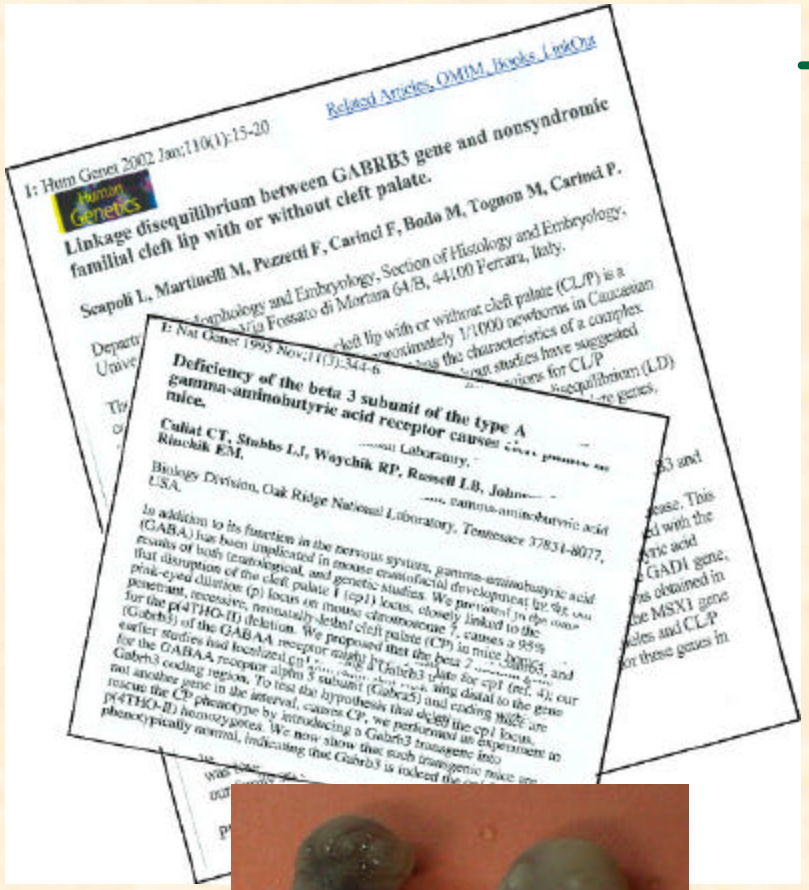

- A recent publication (Scapoli et al., 2002, Human Genetics) has linked the GABRB3 gene to non-syndromic cleft lip and palate in man. The major role of this gene in facial clefting was first demonstrated at ORNL using a series of mouse mutations and gene rescue experiments (Culiat *et al.,* 1995, Nature Genetics) . This earlier work was cited as a rationale for pursuing GABRB3 as a candidate gene in human genetic studies.

- The ORNL mutant mouse resource continues to provide valuable animal models for common facial anomalies in man.

- A new locus (*I7R6*) with at least six ENU-induced mutations has been identified in mouse chromosome 7 (Rinchik et al., 2002, PNAS) and mutants manifest skull and spinal defects.

- Molecular analysis suggests that *I7R6* is *Nell1*, a gene that codes for a ligand in a novel cell-signaling pathway. Human NELL1 is associated with craniosynostosis, a birth defect involving premature fusion of the bones in the developing skull.

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Facial clefting is a very common human congenital defect (1/1000 births), and the search for genes with major roles in causing this complex medical condition has been facilitated by the use of mouse mutations. A recent publication by Scapoli et al. [Human Genetics, 2002, 110(1):15-20] has shown that the gene coding for the human b3 subunit of the g-aminobutyric acid receptor (GABRB3) gene is involved in non-syndromic familial cleft lip with and without cleft palate. The potential role of this gene in cleft palate was initially demonstrated in mice in Gene Rinchik's lab at ORNL (Culiat et al., 1995 Nature Genetics, 11:344-346) and was cited by Scapoli et al. as one of the reasons for focusing on GABRB3 as a candidate gene. The study linking human GABRB3 to facial clefting showcases the power of using the mouse as a system for providing hints into the genetic basis of human diseases. In fact, Scapoli et al tested five candidate genes suggested by various genetic and molecular analyses of mouse mutations and GABRB3 indicated the strongest linkage in the population used by the researchers.

The conservation of biological processes controlling facial development (as illustrated by the human GABRB3/mouse *Gabrb3* studies) suggests that additional features of human craniofacial development can be dissected using mouse models. Recently, work conducted in C. T. Culiat's lab at ORNL has shown that ethylnitrosourea (ENU)-induced mutations of a new locus in mouse chromosome 7 (*l7R6*, Rinchik et al., 2002, PNAS, 99:844-849) are alterations of the novel protein kinase C binding protein *Nell1*. Human NELL1 is associated with a birth defect (1/2500 births) called craniosynostosis, a premature fusion of bones in the developing skull. Mouse *l7R6/Nell1* mutants display skull and spinal defects and are potential models for understanding the molecular basis of craniosynostosis. Moreover, the NELL1 protein is predicted to be a ligand for a novel cell-signaling pathway in brain and skull development. Consequently the new *l7R6/Nell1* mutants (six confirmed alleles, two being tested) will serve as key reagents for functional annotation of the human sequence and for models of the human disease.

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