# Developmental systems genomics identifies expression quantitative trait loci underlying strain differences in skeletal differentiation and developmental pace

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Orofacial clefts are the most common facial anomaly in humans, affecting 1/700 births worldwide. Mouse models provide a critical platform for human disease allele discovery owing to recent developments in gene editing that enable rapid validation of novel variants. However, multiple published examples demonstrate the profound effect that mouse genetic background can have on the penetrance and expressivity of craniofacial phenotypes. Thus, our limited understanding of the effect of natural strain variation on developmental processes presents a major challenge to validation of disease variants and our ability to model human congenital malformations. Significantly lacking are experimental models that accurately relate genomic sequence variation to variation in transcriptional dynamics that drive morphogenesis and the potential for pathological outcomes. Diversity Outbred mice combine the genetic and phenotypic diversity present in 8 inbred founder strains of laboratory mice to generate highly heterozygous mice optimized for use in systems-level genetic dissection of complex traits. Addressing the unique challenges genetically diverse mice pose for developmental studies, we report the first implementation of a systems genomics approach within the context of embryogenesis. We leveraged this novel experimental framework to systematically dissect the impact of genetic variation on development of the secondary palate and to genetically map loci influencing skeletal differentiation, developmental pace, and palate/facial morphology. Ongoing studies will provide diagnostic insight into individual gene contribution to the etiology of craniofacial birth defects and advance understanding of emergent functions of gene networks that provide constraint on genetic variation to define thresholds separating normal from pathological shape variation.