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Developmental mechanisms underlying variation in craniofacial disease and evolution

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ABSTRACT

Craniofacial disease phenotypes exhibit significant variation in penetrance and severity. Although many genetic contributions to phenotypic variation have been identified, genotype–phenotype correlations remain imprecise. Recent work in evolutionary developmental biology has exposed intriguing developmental mechanisms that potentially explain incongruities in genotype–phenotype relationships. This review focuses on two observations from work in comparative and experimental animal model systems that highlight how development structures variation. First, multiple genetic inputs converge on relatively few developmental processes. Investigation of when and how variation in developmental processes occurs may therefore help predict potential genetic interactions and phenotypic outcomes. Second, genetic mutation is typically associated with an increase in phenotypic variance. Several models outlining developmental mechanisms underlying mutational increases in phenotypic variance are discussed using *Satb2*-mediated variation in jaw size as an example. These data highlight development as a critical mediator of genotype–phenotype correlations. Future research in evolutionary developmental biology focusing on tissue-level processes may help elucidate the "black box" between genotype and phenotype, potentially leading to novel treatment, earlier diagnoses, and better clinical consultations for individuals affected by craniofacial anomalies.

1. Introduction

Craniofacial anomalies are among the most common and debilitating human congenital disorders. They impose many challenges on affected individuals, their families, and society at large in terms of both economic costs and socio-psychological effects. Treatment for craniofacial anomalies often requires multiple surgical interventions and has significant long-term health implications for affected individuals. As such, there is understandably great interest in the prevention and early identification of craniofacial anomalies, as well as anticipating potential related disease phenotypes. In particular, the possibility of predicting disease phenotypes from the genome is an appealing goal (Claes et al. 2014). That such a concept is even conceivable is due to recent technical advances in both genotyping and phenotyping. Over the past 25 years, advances in genomics and sequence analysis, fueled in part by the human genome project, have produced an extensive understanding of human genetic diversity. In contrast, phenotypic information has been more challenging to precisely define because shape data is complex and multivariate in nature. In order to quantify phenotype, facial shape must first be captured, which has been done using a variety of imaging methods (e.g., digital photography, micro-computed tomography, optical projection tomography, and cone beam computed tomography). Shape images are then measured, which can also be done in several ways (e.g., linear distance measurement between anatomical landmarks (traditional morphometrics), assigning cartesian coordinates of homologous anatomical landmarks (geometric morphometrics), and analyses of shape outlines (elliptical Fourier analysis)). Finally, data acquired using any of these methods must be analyzed using a corresponding set of multivariate statistical methods (methodologies reviewed in Bookstein (1996), Cooper and Albertson (2008) and Hallgrimsson et al. (2015)).

With these advances in quantitative phenotyping methodologies, investigations relating specific genotypes to both normal and abnormal craniofacial phenotypes have been undertaken. The FaceBase Consortium (www.facebase.org) was launched in 2009, with a major goal being to better understand the genetics underlying craniofacial development and malformation. This initiative aims to integrate multiple datasets, including variation in genotype, phenotype, and gene expression, from multiple species at multiple developmental stages (Hochheiser et al. 2011). Several other groups have used genome wide association studies (GWAS) to map genetic variants in humans to facial phenotypes (Coussens

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and van Daal, 2005; Boehringer et al., 2011; Liu et al., 2012; Paternoster et al., 2012; Claes et al., 2014). While there is still much work to be done, the early results have confirmed the intricacy of genotype–phenotype relationships in craniofacial development. In fact, rather than clarifying genotype–phenotype correlations, the data indicate that precise genome based phenotypic predictions are probably not realistic (Hallgrimsson et al., 2014). For example, the application of quantitative morphometrics to embryonic craniofacial development has broadened our comprehension of variation in morphogenesis (e.g., Young et al., 2007, 2010, 2014; Parsons et al., 2008; Martinez-Abadias et al., 2012). These studies have revealed that subtle phenotypic variation occurs even in isogenic populations such as genetically identical, inbred littermate mice, highlighting the relevance of non-genomic contributions to phenotype (Parsons et al., 2008; Hallgrimsson et al., 2009).

There are numerous reasons why genotype and phenotype relationships are imprecise (see Hallgrimsson et al. (2014) for a detailed discussion). Many of the complicating factors can be attributed to the genome itself, particularly epistatic interactions. However, it is also widely understood that developmental processes influence phenotypic variation by mediating genetic interactions with the environment (Waddington, 1957; Hall, 1999). Identical genotypes can produce phenotypic diversity in response to environmental heterogeneity (phenotypic plasticity) and/or random variation in developmental processes (developmental noise). While the precise mechanisms underlying phenotypic plasticity and developmental noise are not entirely understood, these phenomena have been widely studied in the field of evolutionary developmental biology (evo-devo). Many research programs in evo-devo are explicitly focused on phenotypic plasticity, that is, the potential for a given genotype to produce multiple, subtly different phenotypes. In other words, studies in evo-devo investigate precisely those mechanisms that cause deviations in genotype–phenotype correlations, and insights from these studies potentially contribute to our understanding of variation in phenotypic penetrance of disease.

In this review, I will focus on two general observations from studies in evo-devo that provide insight into the complexity of genotype–phenotype relationships. The first observation is that, rather than directly causing specific phenotypes, genes provide products that contribute to developmental processes (Smith and Schneider, 1998; Hallgrimsson et al., 2009, 2014). Multiple genes contribute to the regulation of relatively fewer developmental processes, and phenotypic outcomes ultimately derive from the orchestration and interaction of these developmental processes (Fig. 1). The second observation I will discuss is that genetic mutation is often associated with an increase in phenotypic variance (Dunn and Fraser, 1958; Scharloo, 1991; Hallgrimsson et al., 2006). To address how these observations from evo-devo may help predict potential genetic interactions and phenotypic outcomes relevant to craniofacial disease, I first describe major developmental processes in craniofacial development and how molecular and cellular processes underlying them contribute to both normal and abnormal facial variation. Then, using the transcription factor *Satb2* as an example, I describe developmental mechanisms that may explain how genetic mutation can amplify developmental noise to increase variance in phenotypic outcomes.

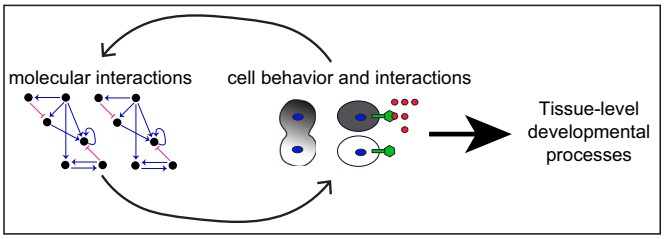

Fig. 1. Molecular and cellular interactions regulate tissue-level processes. Many genes are simultaneously expressed in each cell, and it is the sum of genetic interactions that regulates cellular behavior and interactions. Cellular behavior also feeds back onto gene expression. For example, cell division can affect gene expression through the asymmetric division of molecular components or by altering the position of cells relative to extracellular signals. Together, these molecular and cellular interactions contribute to tissue-level developmental processes.

2. Developmental processes and craniofacial variation

The number of genes known to contribute to craniofacial development continues to grow, while the impact of individual genes on normal craniofacial variation is relatively small (Liu et al., 2012; Hardy and Singleton, 2009; Manolio et al., 2009). This suggests that multiple genes have additive effects on interrelated developmental processes. Developmental processes are driven by cellular behavior (e.g., mitosis, apoptosis) and character (e.g., receptor expression, ligand production), which result from the sum of all gene expression within a given cell. Cellular behavior also feeds back on molecular interactions because gene expression can change as the result of cell behavior. For example, cell division may alter gene expression through differential inheritance of asymmetrically distributed molecules and/or as a result of cell movement after division that modifies the relationship of individual cells to external signals (Fig. 1). These processes, in which inductive and morphogenetic mechanisms occur simultaneously, are considered to be morphodynamic (Salazar-Ciudad and Jernvall, 2004). Morphodynamic processes amplify genotype–phenotype complexity because stochastic events in the spatiotemporal organization of cells and/or extracellular molecules subsequently impact tissue-level developmental processes and introduce phenotypic variation (Salazar-Ciudad and Jernvall, 2004).

Compared to the genetic complexity of craniofacial development, relatively few tissue-level developmental processes critical to normal facial development have been identified (Fig. 2). Investigating when and how molecular and cellular variation alters these processes may provide insight into how genetic mutation contributes to variation in the penetrance and severity of craniofacial disease (see Table 1). Key processes in craniofacial development include cranial neural crest (CNC) development (e.g., induction, specification, delamination, migration), morphogenesis (e.g., patterning, growth, and fusion of the facial primordia), and histogenesis (e.g., tissue differentiation) (Fig. 2). A brief overview of the molecular and cellular regulation and variation in these processes in vertebrate evolution as well as examples of how disruption in these processes contributes to disease is presented below.

2.1. Cranial neural crest development

The evolution of the vertebrate head was facilitated by the evolution and elaboration of CNC, a multi-potent and migratory population of stem/progenitor cells (Gans and Northcutt, 1983; Northcutt, 2005). CNC development involves multiple processes, including induction, specification, epithelial-mesenchymal transition (EMT), delamination, and migration (Fig. 2A; Sauka-Spengler and Bronner-Fraser 2008; Betancur et al. 2010). Induction of cells competent to generate CNC occurs at the neural plate border between the presumptive neural and ectodermal cells. Induction is initiated by a number of extrinsic signals, including members of the Bone morphogenetic protein (BMP), Wnt, Delta/Notch, and Fibroblast growth factor (Fgf) signaling pathways that turn on genes regulating specification of true CNC in the dorsal neuroepithelium (Sauka-Spengler and Bronner-Fraser, 2008). After specification, CNC delaminate, undergo EMT, and migrate away from

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