Neural crest and the origin of species-specific pattern

Richard A. Schneider

Summary
For well over half of the 150 years since the discovery of the neural crest, the special ability of these cells to function as a source of species-specific pattern has been clearly recognized. Initially, this observation arose in association with chimeric transplant experiments among differentially pigmented amphibians, where the neural crest origin for melanocytes had been duly noted. Shortly thereafter, the role of cranial neural crest cells in transmitting species-specific information on size and shape to the pharyngeal arch skeleton as well as in regulating the timing of its differentiation became readily apparent. Since then, what has emerged is a deeper understanding of how the neural crest accomplishes such a presumably difficult mission, and this includes a more complete picture of the molecular and cellular programs whereby neural crest shapes the face of each species. This review covers studies on a broad range of vertebrates and describes neural-crest-mediated mechanisms that endow the craniofacial complex with species-specific pattern. A major focus is on experiments in quail and duck embryos that reveal a hierarchy of cell-autonomous and non-autonomous signaling interactions through which neural crest generates species-specific pattern in the craniofacial integument, skeleton, and musculature. By controlling size and shape throughout the development of these systems, the neural crest underlies the structural and functional integration of the craniofacial complex during evolution.

KEYWORDS
cranial neural crest, craniofacial development, evolutionary-developmental biology, quail-duck chimeras, quck, species-specific pattern, tissue-interactions

1 | INTRODUCTION
The notion that neural crest cells generate species-specific pattern has a long and colorful history. Some of the earliest indications first arose from surgical transplantation experiments designed to exploit pigment variations in amphibian embryos. Around the beginning of the 20th Century, embryologists such as Born (1896), Harrison (1898, 1903), and Spemann (1918) pioneered the use of chimeras, that is combining components from distinct animal species, to follow the movements and fates of cells, and understand the inductive properties of tissues (Harrison, 1935; Mangold, 1923; Mangold & Seidel, 1927; Noden, 1984; Spemann, 1938; Spemann & Mangold, 1924). Their reliance on intrinsic differences in the number, distribution, and color of intracellular pigment granules as a means to keep track of donor versus host tissues was actually a proxy for a neural crest-derived lineage (i.e., melanocytes), something which was suggested by Harrison (1910) and others but which remained debatable at the time (Dorris, 1938; DuShane, 1934, 1935, 1938, 1939; Harrison, 1969; Holtfreter, 1933; Raven, 1931). Soon thereafter, numerous efforts were underway to determine the extent to which neural crest cells establish inter- and intra-specific pigment patterns and to sort out the effects and/or role of interactions with epidermis (Clark Dalton, 1950; Harrison, 1935; Hörstadius, 1950; Macmillan, 1976). For example, neural crest transplants among the tiger salamander, spotted salamander, or white and black strains of the Mexican salamander revealed that “the characteristic adult spots of the graft are in most cases distinctly different from those of the host, and are similar to those of donor adults” (DuShane, 1935, p. 25). Other interspecific transplants also confirmed this finding (Twitty, 1936, 1945; Twitty & Bodenstein, 1939). Thus, what became evident was that “the type of pattern as a whole depends upon...”
qualities intrinsic to the crest-cells” (Hörstadius, 1950, p. 75). What remained unknown was if the neural crest was playing a comparable role in providing species-specific patterning information for any of its other derivatives, something that chimeras could help resolve.

Chimerism was all the rage at the dawn of experimental embryology given its great potential to reveal morphogenetic mechanisms during normal development that lead to the progressive integration of ectoderm, mesoderm, and endoderm; but also, because chimerism could provide a window into the developmental basis for evolutionary variation among species. In his comprehensive review, “Heteroplastic Grafting in Embryology” Harrison (1935) claimed with regard to making chimeras that, “the applicability of the method rests upon the fact that there are related species that differ from one another in pigmentation, rate of growth and development, ultimate size, relative time of appearance of organs, or even in the presence or absence of organs, while at the same time their tissues show a mutual tolerance when combined in one organism” (Harrison, 1969, p. 216). Results of these chimeric transplants among different taxa (i.e., species, genera, families, and even orders such as frogs and salamanders) indicated that some donor tissues did not convey species-specific information.

Harrison (1935) further described conclusions from a broad range of studies and stated that, “In general, inducers are not specific...But the induced organ has entirely the character of the species from which it is developed” (Harrison, 1969, p. 217). For example, in classic “organizer” studies (Spemann, 1918, 1938; Spemann & Schottke, 1932), where some of the donor tissues were from salamander endoderm, the induced mouth parts remained frog-like leading to Speemann’s purported description of the conversation between the host ectoderm tissue and its endoderm inducer, “you tell me to make a mouth; all right, I’ll do so, but I can’t make your kind of mouth; I can make my own and I’ll do that” (Harrison, 1933, p. 318).

In contrast, when entire limb buds were exchanged between two species of salamanders with very different rates of development or where the limbs themselves varied greatly in size, the resultant chimeras always had limbs like that of the donor in terms of timing of maturation and morphology (Dettwiler, 1930; Harrison, 1915, 1917, 1924; Schwind, 1932; Swett, 1930). Grafts of other embryonic rudiments and whole organs such as the eye, ear, heart, teeth, or gills produced equivalent results (Copenhaver, 1930; Harrison, 1929, 1935; Huxley, 1932; Kaan, 1930; Richardson, 1932; Stone, 1930; Twitty, 1930, 1932, 1934; Twitty & Schwind, 1931), with the conclusion being that somewhere within a composite organ resided the source of species-specific pattern.

Subsequent explorations of the relative contributions of the constituent parts of these composite organs began to shed light on this issue, particularly with regard to the requisite role for derivatives of each of the three germ layers. In the case of the eye, the lens (from surface ectoderm) and the optic cup (from neural ectoderm) were mutually regulating (Harrison, 1929, 1935; Stone & Dinnean, 1940; Twitty, 1930, 1932), whereas host eye muscles (from paraxial mesoderm) were subservient to the eye itself and would accommodate the size, orientation, and location of the donor eye (Twitty, 1930, 1932, 1934, 1966). In the case of the forelimb, the mesoderm, which produces the muscles and skeleton, would always determine its size, shape, and growth rate, whereas the ectoderm had limited influence (Harrison, 1935; Rotmann, 1931, 1933; Schwind, 1931, 1932).

Like what had been observed for pigment patterns, the gills or branchial system of the pharynx provided clear evidence for a dominant role of neural crest-derived mesenchyme not only in generating the jaw and gill cartilages themselves (Landacre, 1921; Platt, 1891, 1893, 1898; Stone, 1922, 1926, 1929) but also in determining their species-specific pattern (De Beer, 1947; Harrison, 1935). In addition to the neural crest skeletal derivatives, the gill arches contain a pouch lined by endoderm, muscles from the mesoderm, and an outer epithelium from the ectoderm (De Beer, 1937; Goodrich, 1913, 1918, 1930). Numerous grafting experiments of each of these constituents either separately or in various combinations (Adams, 1931; Harrison, 1921, 1935; Holtfreter, 1936; Rotmann, 1931, 1933; Severinghaus, 1930; Spemann, 1921; Stone, 1932) showed that the ectoderm, mesoderm, and endoderm had mixed and inconsistent effects on the size, shape, and rate of development of the external gills.

In stark contrast, were the neural crest cells, which according to Harrison (1935) were “Far more conclusive” and had “a profound effect upon the development of the branchial system, particularly the visceral skeleton” (Harrison, 1969, p. 233). For example, transplants of neural crest from a larger species of salamander in place of neural crest from a smaller species gave rise to pharyngeal arches with the size and shape of the donor species (De Beer, 1947; Harrison, 1933; Hörstadius, 1950). Other neural crest transplants among frogs and salamanders also produced donor-like cartilages in the pharyngeal arches and jaw skeleton (Andres, 1949; Fassler, 1996; Hall & Hörstadius, 1988; Hörstadius & Sellman, 1941, 1946; Noden & Schneider, 2006; Raven, 1931, 1933, 1935; Spemann & Schottke, 1932; Wagner, 1959). Early on, such work suggested to scientists like Raven (1933) as conveyed by Hörstadius (1950) that, “the neural crest in the head might have a special task in connection with its movements, as a carrier of inductive influences” (p. 93). This classic body of literature demonstrated clearly that, “transplanted neural crest cells express a species-specific patterning that is an intrinsic property of the skeletogenic cells” (Hall, 1999, p. 71). Moreover, this initial work garnered a much deeper appreciation for the hierarchical levels of organization within these complex developmental organ systems and pointed to the key role for neural crest cells in the evolution of species-specific morphology.

By the turn of the 21st Century, other transplant experiments in non-amphibian taxa such as among mouse, human, chick, or quail (Cohen et al., 2016; Fontaine-Perus, 2000; Fontaine-Perus & Cheraud, 2005; Fontaine-Perus, Cheraud, & Halgand, 1996; Fontaine-Perus et al., 1997; Kirby, Stadt, Kumiski, & Herlea, 2000; Lwigale & Schneider, 2008; Mitsuhashi, Caton, & Cobourne, 2006; Mitsuhashi, Cheraud, Sharpe, & Fontaine-Perus, 2003; Pudliszewski & Pardanaud, 2005; Serbedzija & McMahon, 1997); among divergent species of birds including quail, chick, duck, and emu (Ealba et al., 2015; Eames & Schneider, 2005, 2008; Fish & Schneider, 2014a, 2014b; Fish, Sklar, Woronowicz, & Schneider, 2014; Hall et al., 2014; Jheon & Schneider, 2009; Le Douarin, Dieterlen-Lievre, Teillet, & Ziller, 2000; Merrill, Eames, Weston, Heath, & Schneider, 2008; Schneider, 2005, 2015; Schneider & Helms, 2003; Sohal, 1976; Solem, Eames, Tokita, & Schneider, 2011; Tokita & Schneider, 2009; Tucker & Lumsden, 2004;
the sections below. Such work, which has helped illuminate the or-
ts of the craniofacial complex become structurally and functionally

ectoderm (e.g., feathers and egg teeth) and mesoderm (e.g., muscles,

which the cranial neural crest directs the patterning of its own deriv-
atives (e.g., cartilages, bones, tendons), as well as those arising from
ectoderm (e.g., feathers and egg teeth) and mesoderm (e.g., muscles,

blood vessels, osteoclasts) in order to understand how the major sys-
tems of the craniofacial complex become structurally and functionally

integrated during development and how they become modified during
evolution (Figure 1a). Such work, which has helped illuminate the ori-
gin of species-specific pattern, is summarized and contextualized in
the sections below.

2 | ORIGIN OF SPECIES-SPECIFIC VERSUS SPECIES-GENERIC ASPECTS OF PATTERN

When describing species-specific pattern, what is typically meant are
those relatively unique morphological or behavioral features of an
organism that often appear well-suited to meet certain functional, eco-
logical, sexual, or other kinds of selective pressures. Moreover, such
features can be defining and used to distinguish one species (or higher
taxonomic level) from another. In this context, and in terms of morphol-
ogy, a type of species-specific pattern that has long been of central
concern pertains to changes in size and shape during development and
evolution (Fish & Schneider, 2014b; Schneider, 2015, 2018). This focus
was most significantly catalogued and detailed over 100 years ago by
Thompson (1917) in his celebrated tome, On Growth and Form. Using a
geometric system of Cartesian coordinates, Thompson strove to
describe transformations in the size and shape of organs and organisms
during the growth of individuals and across different species. In so
doing, he helped spawn an entire discipline of morphometrics that con-
tinues to this day (Arthur, 2006; Benson, Chapman, & Siegel, 1982;
Bookstein, 1978, 1990; Gayon, 2000; Hallgrimsson et al., 2015; Mar-
cus, 1996; Schneider, 2018; Siegel & Benson, 1982; Stern & Emlen,
1999; Zelditch, 2004).

Since Thompson, many other scientists have endeavored to
address the origins of species-specific size and shape through

mathematical, theoretical, and experimental means, ultimately in
search of underlying genetic, molecular, cellular, or other developmen-
tal mechanisms including allometry and heterochrony (Alberch, 1982a,
1985, 1989; Alberch, Gould, Oster, & Wake, 1979; Anderson & Busch,
1941; Atchley, Rutledge, & Cowley, 1981; Bertalanffy & Pirozynski,
1952; Clark & Medawar, 1945; Copping & Coppinger, 1982; Cop-
pinger & Schneider, 1995; De Beer, 1930; De Renzi, 2009; Drake,
2011; Godfrey & Sutherland, 1995; Gould, 1966, 1971, 1977; Hersh,
1934; Huxley, 1932, 1950; Huxley & Teissier, 1936; Kermack &
Haldane, 1950; Klingenberg, 1998; Lande, 1979; Lord, Schneider, &
Coppinger, 2016; Lumer, 1940; Minot, 1908; Needham & Lerner,
1940; Oster & Alberch, 1982; Oster, Shubin, Murray, & Alberch,
1988; Reeve, 1950; Rensch, 1948; Roth & Mercer, 2000; Shea, 1985;
Smith et al., 2015; Smith, 2003; Stern & Emlen, 1999; Von Bonin,
1937; Waddington, 1950, 1957). A common theme for much of the
research on size and shape relates to those changes that occur with
respect to developmental time either as a function of age or growth.
Minot (1908) laid the groundwork for this perspective by emphasizing
the importance of cell number, differentiation, and rates of growth in
the regulation of the size of animals and/or their organs. Thompson
(1952) later elaborated on this idea when stating that, “the form of an
organism is determined by its rate of growth in various directions;
hence rate of growth deserves to be studied as a necessary prelimi-
nary to the theoretical study of form, and organic form itself is found,
mathematically speaking, to be a function of time” (p. 79). Thus, given
that the neural crest generates species-specific pattern in the cranio-
facial complex, and this pattern can be defined primarily as the size
and shape of structures, then a critical insight could be gained by
understanding the extent to which the neural crest controls the timing
of events during development. A further question also remains, which
is from where do other aspects of craniofacial pattern (i.e., those that
are not necessarily species-specific) arise?

In addition to their species-specific pattern, structures likewise
possess many more “species-generic” aspects of pattern. These
include their axial orientation (e.g., dorsal-ventral, mediolateral,
proximal-distal, oral-aboral), anatomical identity (e.g., upper versus
lower jaw, eye versus ear), and tissue type (e.g., cartilage, bone, mus-
cle, tendon, nerve). For the most part, epithelia in the craniofacial
complex appear to supply the cues required for the establishment of
generic pattern and express the factors necessary to maintain out-
growth of individual components. For example, signaling by ectoder-
mal epithelium around the frontonasal process (i.e., the primordium
that gives rise to the mid- and upper-face) is essential for proper
expansion and orientation of skeletal elements along the dorsoventral,
mediolateral, and proximodistal axes (Foppiano, HU, & Marcucio,
2007; HU & Marcucio, 2009b; HU, Marcucio, & Helms, 2003). Experi-
mentally rotating epithelium in the frontonasal process can lead to
mirror image duplications of upper beak structures along the dorso-
ventral axis (Helms & Schneider, 2003; HU et al., 2003; Marcucio,
Cordero, HU, & Helms, 2005).

Similarly, endodermal epithelium that lines the pharynx is needed
for the proper axial orientation, anatomical identity, and growth of
cartilage and bone in the lower jaw and hyoid skeleton (Brito, Teillet,
& Le Douarin, 2006; Couly, Creuzet, Bennaceur, Vincent, & Le Douarin,
2002; Crump, Maves, Lawson, Weinstein, & Kimmel, 2004; David,
FIGURE 1  (a) Pseudocolored scanning electron micrograph of a chick in cross-section [modified from Tosney (1982)] through the midbrain/hindbrain boundary and first pharyngeal arch showing progenitors of tissues in the jaw and face. Modified from Ealba et al. (2015). (b) Skull and lower jaw (mandible) of an adult quail and (c) duck in lateral view. Modified from Tokita and Schneider (2009). (d) Unilateral transplant of presumptive quail neural crest from the posterior forebrain (fb), midbrain (mb), and anterior hindbrain (hb) into a duck host. Non-neural surface ectoderm (se) and mesodermal mesenchyme (mm) are shown in dorsal view. Modified from Eames and Schneider (2008). (e) Distinct maturation rates of quail (pink squares) versus duck (purple circles) after being stage-matched at HH9.5 for surgery (red triangle on the Y-axis) result in quail donor cells remaining accelerated by approximately three stages within 2 days after surgery relative to the duck host [modified from Eames & Schneider (2005)]. (f) By stage 25, the frontonasal (fn), maxillary (mx), and mandibular (ma) primordia of quail and (g) duck appear similar in shape but not in size (frontal view). Modified from Schneider (2005). (h) Sagittal section (in plane of white dashed line in panel g) in a chimeric quck through the maxillary (mx) and mandibular (ma) region showing quail donor cells labeled with Q¢PN (black nuclei). Duck-host surface ectoderm (se), pharyngeal endoderm (pe), mesodermal mesenchyme (mm) are unlabeled. The hyoid arch (hy) is also negative since its precursors were not transplanted. Modified from Ealba and Schneider (2013). (i) By HH25, the frontonasal (fn), maxillary (mx), mandibular (ma), and hyoid (hy) primordia (sagittal view) are surrounded by surface ectoderm (se), pharyngeal endoderm (pe) and forebrain neuroepithelium (fb), and contain contributions from the neural crest, nasal placode (np), and cranial ganglia (V, VII, IX). Mesodermal mesenchyme (mm) produces muscles, vascular endothelium, and some skeletal tissues. Modified from Schneider (2005)
Saint-Etienne, Tsang, Schilling, & Rosa, 2002; Delloye-Bourgeois, Rama, Brito, Le Douarin, & Mehlen, 2014; Graham, 2003; Haworth et al., 2007; Kikuchi et al., 2001; Kimmel et al., 1998; Miller, Schilling, Lee, Parker, & Kimmel, 2000; Pietrokovski & Nusslein-Volhard, 2000; Ruhin et al., 2003; Veitch, Begbie, Schilling, Smith, & Graham, 1999.

When endodermal epithelium is rotated surgically or removed, the associated neural crest-derived skeleton follows accordingly (Coully et al., 2002; Haworth et al., 2007). Therefore, both ectodermal and endodermal epithelia function as local sources of signals for generic patterns that elicit and/or maintain programmatic responses from the adjacent neural crest-derived mesenchyme (Creuzet, Coully, & Le Douarin, 2005; Ferguson, Tucker, & Sharpe, 2000; Higashihori, Buchtova, & Richman, 2010; Langille & Hall, 1993; Le Douarin, Creuzet, Coully, & Dupin, 2004; Mitsiadis et al., 2003; Richman & Tickle, 1989; Santagati & Rijli, 2003; Tak, Park, Piao, & Lee, 2017; Tucker, Yamada, Grigoriou, Pachnis, & Sharpe, 1999; Wilson & Tucker, 2004). As will be discussed later, such programmatic responses are in fact species-specific, and they also reciprocally influence the temporal and spatial domains of expression in adjacent epithelia (Eames & Schneider, 2005; Schneider & Helms, 2003).

Pharyngeal endoderm, and neural and non-neural ectoderm function as key epithelial signaling centers by releasing complex combinations of secreted molecules from well-characterized pathways including Bone Morphogenetic Protein (BMP), Sonic Hedgehog (SHH), Fibroblast Growth Factor (FGF), and Wingless-Related (WNT) that are indispensable to the proper patterning and differentiation of neural crest mesenchyme (Alvarado-Mallart, 2005; Anderson, Lawrence, Stottmann, Bachiller, & Klingensmith, 2002; Barlow & Francis-West, 1997: Benouaiche, Gitton, Vincent, Coully, & Levi, 2008; Cela et al., 2016; Crump et al., 2004; Ekker et al., 1995; Francis-West, Ladher, Barlow, & Graveson, 1998; Gitton et al., 2010; Graham, 2003; Marcucio et al., 2005; Marcucio, Young, Hu, & Hallgrimson, 2011; Pera, Stein, & Kessel, 1999; Pietrokovski & Nusslein-Volhard, 2000; Sasaki & De Robertis, 1997; Schneider, Hu, Rubenstein, Maden, & Helms, 2001; Shimamura, Hartigan, Martinez, Puuelles, & Rubenstein, 1995; Veitch et al., 1999; Wilson & Tucker, 2004; Wittington, Beddington, & Cooke, 2001; Xu et al., 2015). Various members and targets of these pathways also become differentially regulated not only as a mechanism to support the outgrowth of the jaw and facial skeletons (Abzhanov & Tabin, 2004; Ashique, Fu, & Richman, 2002a; Chong et al., 2012; Cordero, Schneider, & Helms, 2002; Couly et al., 2002; Doufelí & Mina, 2008; Geetha-Loganathan, Nimmagadda, Fu, & Richman, 2014; Havens et al., 2008; Helms & Schneider, 2003; Hu, Colnot, & Marcucio, 2008; Hu et al., 2003; Liu et al., 2005; MacDonald, Abbott, & Richman, 2004; Melnick, Witcher, Bringas, Carlton, & Jaskoll, 2005; Miller et al., 2000; Mina, Wang, Ivanisiević, Upholt, & Rodgers, 2002; Nimmagadda et al., 2015; Richman, Herbert, Matovinovic, & Walin, 1997; Rowe, Richman, & Brickell, 1992; Schneider, Hu, & Helms, 1999; Schneider et al., 2001; Szabo-Rogers, Geetha-Loganathan, Nimmagadda, Fu, & Richman, 2008; Wada et al., 2005; Young, Chong, Hu, Hallgrimson, & Marcucio, 2010) but also as a component of regulating species-specific size and shape (Abramyan, Leung, & Richman, 2014; Abzhanov et al., 2006; Abzhanov, Protas, Grant, Grant, & Tabin, 2004; Bhullar et al., 2015; Brugmann et al., 2007; Brugmann et al., 2010; Cheng et al., 2017; Foppiano et al., 2007; Grant, Grant, & Abzhanov, 2006; Hu & Marcucio, 2009b, 2012; Hu, Young, Li, et al., 2015; Hu, Young, Xu, et al., 2015; Wu, Jiang, Shen, Widellitz, & Chuong, 2006; Wu, Jiang, Sukswaeng, Widellitz, & Chuong, 2004; Young et al., 2014).

Other epithelial tissues that are derived from surface (i.e., non-neural) ectoderm also function as critical patterning centers in conjunction with cranial neural crest. In particular, cranial placodes that contribute to sensory ganglia and sense organs such as the olfactory, optic, otic, trigeminal, and epibranchial systems require repeated and reciprocal interactions with adjacent neural crest mesenchyme for their proper morphogenesis (Baker & Bronner-Fraser, 2001; Bancroft & Bellairs, 1977; Couly & Le Douarin, 1988; Francis-West, Ladher, & Schoenwolf, 2002; Ladher, O'Neill, & Begbie, 2010; Lwigale, 2001; Pispas & Thesleff, 2003; Song, Hui, & Richman, 2004; Szabo-Rogers et al., 2008; Webb & Noden, 1993).

Members and targets of the FGF, BMP, WNT, and other pathways mediate complex signaling interactions among the developing placodes, mesoderm, endoderm, and the neural crest, which in turn lead to the differential activation of placode-specific sets of transcription factors (Anwar, Tambalo, Ranganathan, Grocott, & Streit, 2017; Baker, Stark, Marcelle, & Bronner-Fraser, 1999; Brunkell et al., 2014; Depew et al., 1999; Grocott, Johnson, Bailey, & Streit, 2011; Groves & Bronner-Fraser, 2000; Hintze et al., 2017; Jourdeuil & Taneyhill, 2018; Ladher, 2017; Ladher, Wright, Moon, Mansour, & Schoenwolf, 2005; McLaren, Lutsiou, & Streit, 2003; Moody & Lamantia, 2015; Saint-Jeannet & Moody, 2014; Steventon, Mayor, & Streit, 2014; Yang et al., 2013). In almost all of these cases, the neural crest plays an obligatory role during proper patterning and differentiation.

As neural crest cells migrate throughout the craniofacial complex and settle adjacent to these different types of epithelia they respond by expressing a broad range of transcription factors and other genes that affect their anatomical identity (Ballanger, Mutter, Gruss, & Kessel, 1989; Clouthier et al., 2000; Creuzet, Coully, Vincent, & Le Douarin, 2002; Depew, Luftkin, & Rubenstein, 2002; Gendron-Maguire, Mallo, Zhang, & Gridley, 1993; Grammatopoulos, Bell, Toole, Lumsden, & Tucker, 2000; Hunt, Clarke, Buxton, Ferretti, & Thorogood, 1998; Kimmel et al., 2005; Luftkin et al., 1992; Pasqualetti, Ori, Nardi, & Rijli, 2000; Qiu et al., 1997; Rijli et al., 1993; Rueß, Xiang, Lim, Levi, & Clouthier, 2004; Schilling, 1997; Smith & Schneider, 1998; Tavares, Cox, Maxson, Ford, & Clouthier, 2017). Modulating the levels of various molecules expressed by these epithelia, such as retinoic acid and the BMP antagonist Noggin, can for example, transform one facial primordium into another (Lee, Fu, Hui, & Richman, 2001; Richman & Lee, 2003) ostensibly by altering the gene regulatory networks within the responding neural crest cells.

Moreover, combinatorial expression of homeobox genes such as those in the Hox cluster and other transcription factors affect the ability of neural crest cells from the posterior hindbrain to form appropriate anatomical pattern in the hyoid and subsequent arches (Couly & Le Douarin, 1990; Trainor & Krulmala, 2000; Trainor & Krulmala, 2001). In contrast, neural crest cells from the midbrain and anterior hindbrain that migrate into the frontonasal, maxillary, and mandibular primordia do not rely on Hox genes (Couly et al., 2002; Couly, Grapin-Botton, Coltey, Ruhi, & Le Douarin, 1998; Hunt & Krulmala, 1991; Hunt, Wilkinson, & Krulmala, 1991). If these midbrain and anterior hindbrain populations of neural crest cells are surgically rotated by 180° in order to transpose frontonasal and mandibular precursors,
they generate facial and jaw skeletons that are appropriate for their new location, which reinforces the idea that anatomical identity is established locally (Noden, 1983) in response to epithelial signals.

Along similar lines, if the Hox code is deleted from neural crest cells destined to form the hyoid arch either by grafting non-Hox-expressing mandibular or frontonasal neural crest in place of hyoid arch neural crest cells, or by knocking down Hoxa2, then hyoid arch skeletal elements become replaced by mandibular structures (Gendron-Maguire et al., 1993; Noden, 1983; Rijli et al., 1993; Trainor, Ariza-McNaughton, & Krumlauf, 2002; Trainor, Melton, & Manzano, 2003). Conversely, over-expressing Hoxa2 in mandibular arch neural crest cells gives rise to hyoid skeletal structures instead of mandibular ones (Grammatopoulos et al., 2000; Pasqualetti et al., 2000). Also illustrating the necessity of signaling interactions between the neural ectoderm and the adjacent neural crest, Hoxa2 is downregulated by FGF8, and ectopic expression of Fgf8 in the hindbrain disrupts the pattern of hyoid arch structures (Creuzet et al., 2002; Trainor, Ariza-McNaughton, et al., 2002). Thus, ongoing and reciprocal interactions between epithelia derived from the ectoderm and endoderm, and neural crest mesenchyme lead to the activation of intrinsic transcription factor modules that establish a more species-generic type of pattern, specifically the axial orientation and anatomical identity of craniofacial structures.

Such a conclusion is further supported by experiments that alter combinatorial codes of transcription factors including the Dlx genes, and that genetically manipulate signaling pathways such as endothelin, which affect the axial pattern, outgrowth, and in some instances switch the anatomical identity of the maxillary and mandibular regions of the vertebrate head (Gans & Northcutt, 1983; Northcutt, 2004; Schneider, 2005; Young et al., 2014) in the pharyngeal and oral regions of the vertebrate head (Gans & Northcutt, 1983; Northcutt, 2005; Northcutt & Gans, 1983), the lateral wall of the mammalian skull (Schneider, 1999; Smith & Schneider, 1998), and during the process of domestication (Lord et al., 2016; Sanchez-Villagra, Geiger, & Schneider, 2016; Wilkins, Wrangham, & Fitch, 2014).

In fact, as described below, the degree to which neural crest cells convey species-specific patterning information, and the intrinsic mechanisms that they use, have been made most evident by leveraging chimeric transplant systems that exploit evolutionary differences among birds. Recent research in this area has begun to paint a clearer picture of how individual structures within the craniofacial complex acquire their species-specific pattern, and notably, such work illustrates how developmental programs can become modified internally on the molecular and cellular levels so that morphological variation can be generated in a manner essential for evolution.

3 | ORIGIN OF SPECIES-SPECIFIC PATTERN AS REVEALED BY AVIAN CHIMERAS

Much like prior studies involving chimeras between different amphibian species, a well-established and very useful experimental approach for investigating the developmental origins and patterning of craniofacial structures in amniote embryos has been the use of the quail-chick...
chimeric system (Baker, Bronner-Fraser, Le Douarin, & Teillet, 1997; Borue & Noden, 2004; Cobos, Shimamura, Rubenstein, Martinez, & Puelles, 2001; Couly & Le Douarin, 1990; Couly, Coltey, & Le Douarin, 1992; Couly, Coltey, & Le Douarin, 1993; Köntges & Lumsden, 1996; Le Douarin, 1973; Le Lièvre, 1978; Le Lièvre & Le Douarin, 1975; Noden, 1978b, 1983, 1986a; Noden & Schneider, 2006; Olivera-Martínez, Coltey, Dhouaïli, & Pourquié, 2000; Schneider, 1999; Schneider et al., 2001; Selleck & Bronner-Fraser, 1995). Quail and chick are closely related birds with similar rates of growth and morphology (Ainsworth, Stanley, & Evans, 2010; Fitzgerald, 1969; Hamburger & Hamilton, 1951; Nakane & Tsuzuki, 1999; Padgett & Ivey, 1960; Smith et al., 2015; Zacchei, 1961). Surgical transplants between them have enabled the fates, functions, and behaviors of different cells and tissues to be observed throughout embryogenesis, and this has been indispensable to understanding countless facets of developmental biology (Abramyan & Richman, 2018; Le Douarin & McLaren, 1984; Le Douarin & Dieterlen, 2013; Le Douarin, Dieterlen-Lievre, & Teillet, 1996; Noden, 1984; Noden & Schneider, 2006).

The success of the quail-chick chimeric system stems from the fact that in general, avian embryos are easily accessible in ovo for all kinds of experimental manipulations. This includes grafting or extirpation of tissues through microsurgery, labeling of cells for lineage analysis, implantation of reagent-soaked beads, injection of biochemicals, and manipulation of gene expression via retroviral infection or electroporation (Cerny, Lwigale, et al., 2004; Chen et al., 1999; Elba et al., 2015; Eichele,Tickle, & Alberts, 1984; Fekete & Cepko, 1993; Fish & Schneider, 2014a; Fish et al., 2014; Hall et al., 2014; Johnston, 1966; Krull, 2004; Kulesa, Bronner-Fraser, & Fraser, 2000; Larsen, Zeltser, & Lumsden, 2001; Logan & Tabin, 1998; Lwigale, Conrad, & Bronner-Fraser, 2004; Lwigale, Cressy, & Bronner-Fraser, 2005; Lwigale & Schneider, 2008; Momose et al., 1999; Nakamura & Funahashi, 2001; Noden, 1975; Schneider et al., 2001; Serbedzija, Bronner-Fraser, & Fraser, 1989; Stocker, Brown, & Ciment, 1993; Woronowicz et al., 2018). One advantage of working in birds is that after surgery or other manipulations, eggs can simply be resealed and incubated until the embryos reach stages appropriate for further analysis.

Another factor contributing to the success of avian chimeric systems is that embryos from different avian species can be readily stage-matched using an approach that relies on external morphological characters and that is independent of body size and incubation time (Hamilton, 1965; Ricklefs & Starck, 1998; Starck & Ricklefs, 1998). The Hamburger and Hamilton (HH) staging system, initially created for chick, is the accepted standard (Hamburger & Hamilton, 1951). Other staging systems have been published for quail (Ainsworth et al., 2010; Nakane & Tsuzuki, 1999; Padgett & Ivey, 1960; Zacchei, 1961) and duck (Koecke, 1958), but embryos of these birds can also be staged using the HH system for chicken (Ainsworth et al., 2010; Le Douarin et al., 1996; Lwigale & Schneider, 2008; Mitgutsch, Wimmer, Sanchez-Villagra, Hahnloser, & Schneider, 2011; Schneider & Helms, 2003; Smith et al., 2015; Starck, 1989; Yamashita & Sohal, 1987; Young et al., 2014). The ease at which embryos of diverse types of birds can be stage-matched has advanced the study of species-specific patterning.

During her early and pioneering neural crest transplant work Le Douarin observed that, “Quail and chick cells, experimentally associated, definitively retain their species characteristics in the chimaera” (Le Douarin & Teillet, 1974, p. 163). Yet, while some examples related to patterning and pigmentation of epidermal appendages, as well as hatching behavior continued to be noted (Balaban, 1997; Balaban, Teillet, & Le Douarin, 1988; Sengel, 1990), for the most part because quail and chick are relatively similar, subtle species-specific differences that may have been induced by donor cells have gone largely undetected. Moreover, determining mechanisms of species-specific pattern was not really the primary goal of most studies that employed quail-chick chimeras. In contrast, other experiments using avian chimeras have included domestic duck as a way to identify those patterning mechanisms that generate species-specific differences (Dhouliaïli, 1967, 1970; Hampe, 1957; Lwigale & Schneider, 2008; Pautou, 1968; Schneider & Helms, 2003; Sohal, 1976; Sohal et al., 1990; Sohal et al., 1985; Tucker & Lumsden, 2004; Waddington, 1930; Waddington, 1932; Yamashita & Sohal, 1986, Yamashita & Sohal, 1987; Zwilling, 1959). Additional studies on species-specific size and control of scaling have also included chimeras between quail and emu (Hall et al., 2014), quail and zebra finch (Chen, Balaban, & Jarvis, 2012), and chick and zebra finch (Uygur et al., 2016).

The quail-duck chimeric transplant system has been especially useful for identifying the molecular and cellular basis for species-specific aspects of pattern and for illuminating the mechanistic contributions of neural crest cells during tissue interactions that facilitate the structural and functional integration of the craniofacial complex (Figure 1b,c). The system itself combines classical grafting techniques and tools in vertebrate embryology that have already been mentioned (e.g., Andres, 1949; Hamburger, 1942; Harrison, 1917, 1921, 1924, 1929, 1935; Spemann, 1918, 1921, 1938; Spemann & Mangold, 1924; Spemann & Schotte, 1932; Twitty, 1934, 1945; Twitty & Schwind, 1931; Waddington, 1930, 1932; Wagner, 1959) with modern molecular and cellular methods and assays (Elba & Schneider, 2013; Fish & Schneider, 2014a; Lwigale & Schneider, 2008). In short, presumptive neural crest cells from the midbrain and anterior hindbrain are transplanted from either quail to duck to create chimeric “quck” or from duck to quail to make chimeric “duall” (Elba & Schneider, 2013; Fish & Schneider, 2014a; Lwigale & Schneider, 2008; Schneider & Helms, 2003) (Figure 1d). In this experimental framework, the ability to exploit chimeras between quail and duck embryos is predicated on three features that distinguish these species of birds.

First, quail and duck embryos and their constituent parts are noticeably different in size and shape, which offers a direct way to resolve if species-specific features are mediated by donor- or host-derived tissues. Second, quail and duck embryos develop at distinct rates (17 versus 28 days) (Figure 1e), which allows the effects of donor cells on the host to be readily assessed simply by looking for species-specific changes to the timing of gene expression, tissue differentiation, and/or other events throughout the embryogenesis of the facial primordia (Figure 1f,g). Moreover, by examining the effects of intrinsic rates of maturation (i.e., differences in developmental time) on changes in morphology (i.e., evolutionary differences in size and shape), the quail-duck chimeric system can help advance the study of the relationship between ontogeny and phylogeny, vis-à-vis the cranial neural crest (Schneider, 2018). Third, as is the case for the quail-chick chimeric system (Le Douarin et al., 1996), there is an antibody...
appendages (Bronner-Fraser, 1994; Cramer, 1991; Hirobe, 1995; Olivera-Martinez, Thelu, & Dhouailly, 2004). As discussed already, whereas in the face and aspects of the neck the dermis originates from neural crest mesenchyme (Couly et al., 1992; Matsuoka et al., 1972; Noden, 1978b, 1986b, 1988; Olivera-Martinez et al., 2000; Sawler, O’Guin, & Saunders, 1954; Lucas & Stettenheim, 1972). The embryos of Japanese quail (Coturnix coturnix japonica) have relatively smaller, tightly arranged, and un-pigmented feather buds (Lucas & Stettenheim, 1972; Pispa & Thesleff, 2003; Sawyer, O’Guin, & Knapp, 1984; Yu et al., 2004).

The embryos of white Pekin duck (Anas platyrhynchos) have relatively larger, more spaced, and pigmented feather buds whereas the embryos of white Pekin duck (Anas platyrhynchos) have relatively smaller, tightly arranged, and un-pigmented feather buds (Lucas & Stettenheim, 1972; Schneider, 2005) (Figure 2b,c). In quail-duck chimeras, where quail donor neural crest cells generate the dermis and duck host ectoderm gives rise to the epidermis, cranial feather pattern acquires the identity of the donor species (Eames & Schneider, 2005). Coincident with the distribution of quail donor neural crest-derived dermis, these chimeric "quail" embryos have unpigmented duck-like feathers. Thus, quail-duck chimeras corroborate the role of the neural crest (and by extension the dermis throughout the integument) as the principal source of species-specific patterning information for cranial feathers. These results align with data from other tissue recombination experiments in the trunk between duck and chick, which also indicated that the dermis was a source of species-

4 ORIGIN OF SPECIES-SPECIFIC PATTERN IN THE CRANIOFACIAL INTEGUMENT

Like what has been described earlier for studies on the pigmentation of amphibians, the ability of neural crest cells to mediate species-specific pattern is most readily apparent in the integument of quail-duck chimeras (Eames & Schneider, 2005; Schneider, 2005; Schneider & Helms, 2003). Moreover, in many ways the integument can serve as a microcosm for understanding how reciprocal epithelial-mesenchymal interactions drive the patterning of a broad range of vertebrate organ systems including the limbs, facial primordia, hair, glands, teeth, and bone (Dunlop & Hall, 1995; Fisher, 1987; Francis-West et al., 1998; Hu et al., 2003; Hughes et al., 2018; Lumsden, 1988; Mitsiadis, Hirsinger, Lendahl, & Goridis, 1998; Pispa & Thesleff, 2003; Richman & Tickle, 1992; Salaun, Salzgeber, & Guenet, 1986; Saunders & Gasseling, 1968; Schneider et al., 1999; Schneider et al., 2001; Sharpe & Ferguson, 1988; Shigetani et al., 2000; Theisleff & Sharpe, 1997; Tonegawa, 1973; Tucker, Al Khamis, & Sharpe, 1998; Wang, Upholt, Sharpe, Kollar, & Mina, 1998; Weddien, 1987). The integument is composed partly of epidermis, which is derived from the non-neural ectoderm and is stratified into multiple layers (Hamilton, 1965; Romanoff, 1960; Yasui & Hayashi, 1967). In amniotes, the uppermost layer of epidermis generally produces the keratinized components associated with epidermal appendages such as feathers, scales, hair, horns, beaks, and egg teeth (Coul & Le Douarin, 1988; Kingsbury, Allen, & Rotheram, 1953; Lucas & Stettenheim, 1972; Pera et al., 1999; Pispa & Thesleff, 2003; Sawyer, O’Guin, & Knapp, 1984; Yu et al., 2004).

The embryos of Japanese quail (Coturnix coturnix japonica) have large, widely spaced, and pigmented feather buds whereas the embryos of white Pekin duck (Anas platyrhynchos) have relatively smaller, tightly arranged, and un-pigmented feather buds (Lucas & Stettenheim, 1972; Schneider, 2005) (Figure 2b,c). In quail-duck chimeras, where quail donor neural crest cells generate the dermis and duck host ectoderm gives rise to the epidermis, cranial feather pattern acquires the identity of the donor species (Eames & Schneider, 2005). Coincident with the distribution of quail donor neural crest-derived dermis, these chimeric “quail” contain long brown and black quail-like feathers assembled among short white duck host feather buds (Figure 2d). Conversely, when duck donor neural crest cells are transplanted into quail hosts, the chimeric "duall" embryos have unpigmented duck-like feathers. Thus, quail-duck chimeras corroborate the role of the neural crest (and by extension the dermis throughout the integument) as the principal source of species-specific patterning information for cranial feathers. These results align with data from other tissue recombination experiments in the trunk between duck and chick, which also indicated that the dermis was a source of species-
FIGURE 2  (a) Cranial feather buds form through interactions between neural crest-derived dermis and overlying epidermis, which in chimeras are derived from donor and host, respectively. At stage 33, there is little evidence for feather development, but by stage 36, feather buds contain dermal condensations and they begin to rise above the surface of the integument. (b) Quail cranial feather buds are large and widely spaced whereas those of (c) duck are smaller and more closely spaced. (d) In chimeric quck, quail-like feathers appear at the long bud stage while those derived from the duck host are still short buds. (e) At stage 33, Bmp2 is not expressed in either the dermis or epidermis. However, in (f) chimeric quck at stage 33 Bmp2 is expressed prematurely in donor-derived dermis as well as in host-derived epidermis like what is observed three stages later in (g) control quail (and duck). Modified from Schneider (2005), Eames and Schneider (2005), and Fish and Schneider (2014b). (h) The beaks of quail embryos are short and blunt whereas those of (i) duck are long and broad. (j) Transplants of presumptive cranial neural crest cells, which are destined to form the beak, from quail donors to duck hosts produce chimeric “quck” embryos with quail-like beak size and shape (asterisk). Note that the quail-like quck has webbed feet (arrow), which is indicative of the duck host. Modified from Schneider (2005). (k) The extent of transformation in chimeras corresponds to the boundary that exists in the skull between those bones and cartilages derived from the cranial neural crest and those formed from mesoderm. Based on a drawing from D. Noden. (l) By stage 35, Meckel’s cartilage and the lower jaw are slightly curved in duck as seen in dorsal view. (m) This curved morphology is maintained on the duck host side of chimeric quck whereas Meckel’s cartilage and the lower jaw appear to straighten out on the donor side and achieve a larger size like that observed in a (n) quail embryo three stages later at stage 38. Modified from Fish and Schneider (2014b)
specific pattern for the feathers (Dhouailly, 1967, 1970). But exactly how does neural crest-derived dermis impose its species-specific will on the epidermis?

To accomplish this task, neural crest-derived dermis executes an autonomous molecular feather program that is not only intrinsic to the donor genome, but also that overrides the epidermal feather program of the host. This phenomenon becomes most readily apparent when examining changes to the spatial and temporal domains of gene expression, and rates of feather bud development in quack and dual chimeras (Eames & Schneider, 2005). In particular, donor neural crest modifies the expression of members and targets of the SHH, BMP, and Delta/Notch pathways, which are well known to regulate normal feather morphogenesis (Ashique, Fu, & Richman, 2002b; Chuong et al., 2001; Chuong, Patel, Lin, Jung, & Widelitz, 2000; Crowe, Henrique, Ish-Horowicz, & Niswander, 1998; Morgan, Orkin, Noramly, & Perez, 1998; Patel, Makarenkova, & Jung, 1999; Pispa & Thesleff, 2003; Ting-Berreth & Chuong, 1996; Widelitz et al., 1997; Yu et al., 2002). In chimeras, each of these signaling pathways shows a significant change in the timing and domains of expression in both the dermis and epidermis corresponding to the species and stage of the donor neural crest.

For example, Bmp2 is one of the earliest genes to be expressed wherever the epidermis begins to thicken into placodes along the presumptive feather tracts as well as in the underlying condensations of wherever the epidermis begins to thicken into placodes along the pre-lung period of development (Chuong & Widelitz, 1996). Thus, neural crest cells exert their species-specific will on the donor genome, but also that overrides the epidermal feather program of the host. This phenomenon becomes most readily apparent when examining changes to the spatial and temporal domains of gene expression, and rates of feather bud development in quack and dual chimeras (Eames & Schneider, 2005). In particular, donor neural crest modifies the expression of members and targets of the SHH, BMP, and Delta/Notch pathways, which are well known to regulate normal feather morphogenesis (Ashique, Fu, & Richman, 2002b; Chuong et al., 2001; Chuong, Patel, Lin, Jung, & Widelitz, 2000; Crowe, Henrique, Ish-Horowicz, & Niswander, 1998; Morgan, Orkin, Noramly, & Perez, 1998; Patel, Makarenkova, & Jung, 1999; Pispa & Thesleff, 2003; Ting-Berreth & Chuong, 1996; Widelitz et al., 1997; Yu et al., 2002). In chimeras, each of these signaling pathways shows a significant change in the timing and domains of expression in both the dermis and epidermis corresponding to the species and stage of the donor neural crest.

This remarkable capacity holds true in reverse as evidenced by dual chimeras where slower-developing duck host-derived epidermis imparts its species-specific pattern on the quack epidermis. For example, Bmp2 is one of the earliest genes to be expressed wherever the epidermis begins to thicken into placodes along the presumptive feather tracts as well as in the underlying condensations of wherever the epidermis begins to thicken into placodes along the pre-lung period of development (Chuong & Widelitz, 1996). Thus, neural crest cells exert their species-specific will on the donor genome, but also that overrides the epidermal feather program of the host. This phenomenon becomes most readily apparent when examining changes to the spatial and temporal domains of gene expression, and rates of feather bud development in quack and dual chimeras (Eames & Schneider, 2005). In particular, donor neural crest modifies the expression of members and targets of the SHH, BMP, and Delta/Notch pathways, which are well known to regulate normal feather morphogenesis (Ashique, Fu, & Richman, 2002b; Chuong et al., 2001; Chuong, Patel, Lin, Jung, & Widelitz, 2000; Crowe, Henrique, Ish-Horowicz, & Niswander, 1998; Morgan, Orkin, Noramly, & Perez, 1998; Patel, Makarenkova, & Jung, 1999; Pispa & Thesleff, 2003; Ting-Berreth & Chuong, 1996; Widelitz et al., 1997; Yu et al., 2002). In chimeras, each of these signaling pathways shows a significant change in the timing and domains of expression in both the dermis and epidermis corresponding to the species and stage of the donor neural crest.

5 | ORIGIN OF SPECIES-SPECIFIC PATTERN IN THE BEAK

As is the case for the integument, quail-duck transplants likewise demonstrate that neural crest cells provide species-specific information for patterning the beak and underlying jaw skeleton, which differ substantially between quail and duck in conjunction with their highly specialized modes of feeding (Figure 2h,i). Quail neural crest cells destined to form the beak skeleton make quail-like beaks on duck hosts and reciprocal transplants of duck neural crest cells generate duck-like bills on quail hosts (Schneider & Helms, 2003) (Figure 2j,k). Equivalent species-specific transformations are observed when neural crest cells fated to become cartilages in the jaw joint are transplanted between quail and duck (Tucker & Lumsden, 2004). Overall, these studies using quail-duck chimeras reinforce the key role for neural crest in establishing species-specific morphology of the beak and jaw apparatus.

However, such results are not really surprising given that the jaw skeleton is derived entirely from the neural crest (Couly et al., 1993; Köntges & Lumsden, 1996; Le Lièvre, 1978; Le Lièvre & Le Douarin, 1975; Noden, 1978b), and also because the long history of chimeric grafting experiments discussed earlier had already revealed the special species-specific properties of this lineage. But gaining the ability to distinguish between beak tissues that arise from the donor versus the host with a high degree of certainty, as well as possessing tools to assay for donor-mediated changes in gene expression, is what sets this modern chimeric strategy apart from earlier studies (Ealba & Schneider, 2013; Fish & Schneider, 2014a; Lwigale & Schneider, 2008; Schneider & Helms, 2003). A first critical insight in this regard came from examining changes to beak tissues derived from the host. For instance, at the tip of their bill, duck have an egg tooth that is a flat epidermal nail, whereas quail develop an egg tooth that is a conical protrusion of hard keratin (Lucas & Stettenheim, 1972). The quack egg tooth, despite arising entirely from non-transplanted duck host epidermis, resembles that found in quail. Similarly, the dual egg tooth looks like that of the duck. This clear transfer of patterning information from donor neural crest to non-neural crest host-derived tissues reveals that the transformation of the beak in chimeras is more-or-less comprehensive and helps explain how the beak can become modified as an integrated morphological unit in its entirety during the course of evolution (Schneider, 2005).

A second important discovery arose after analyzing genes that are known to pattern the face and that also show well-defined periods of expression during development. Because quail and duck have distinct rates of maturation, the initiation and cessation of expression of such genes differ in absolute time. For example, twenty-four hours after surgery, control quail embryos express the transcription factors Barx1 and Msx1 in neural crest-derived mesenchyme of the developing beak primordia, but control duck embryos do not yet express these genes because they require a longer period of time to reach an...
equivalent stage. Correspondingly and quite strikingly in quck chimeras, these genes are expressed in mesenchyme derived from the quail donor but not from the duck host. Similarly, 48 hr after surgery, control quail express Shh but not Pax6 in facial ectoderm whereas control duck express Pax6 but not Shh. In quck chimeras, Shh is found in duck host facial ectoderm but Pax6 is not, which is the pattern observed in quails. As already discussed, Shh expression in the facial ectoderm for instance, is not only mediated by the neural crest (Hu & Marcucio, 2012; Schneider et al., 2001), but also plays a critical role in specifying the axial orientation and maintaining the outgrowth of the facial skeleton (Abzhanov & Tabin, 2004; Ahlgren & Bronner-Fraser, 1999; Chong et al., 2012; Delloye-Bourgeois et al., 2014; Helms et al., 1997; Hu & Helms, 1999; Hu & Marcucio, 2009a; Hu, Young, Li, et al., 2015; Jeong, Mao, Tenzen, Kottmann, & McMahon, 2004; Lan & Jiang, 2009; Young et al., 2010). Thus, such temporal shifts in the onsets and offsets of gene expression supply stark evidence that quail neural crest cells produce quail-like beaks on duck by sustaining their own molecular programs and by modulating the spatial and temporal patterns of gene expression in non-neural crest host tissues such as the adjacent epithelium.

Again, as noted by Raven (1933) and conveyed by Hörstadius (1950), part of the special ability of neural crest to regulate species-specific pattern likely arises “in connection with its movements, as a carrier of inductive influences” (p. 93). Simple parameters such as the amount and distribution of donor neural crest cells throughout the facial primordia appears to modulate gene expression in host epithelium in a dose-dependent manner (Elalb & Schneider, 2013; Merrill et al., 2008; Schneider & Helms, 2003). Once a certain threshold is reached (Woronowicz et al., 2018), neural crest cells ultimately endow structures with species-specific size and shape presumably because their “inductive influences” are mediated at the population level. This scenario is also substantiated by our observation that significant differences exist in the number of jaw precursors that migrate into the mandibular primordia of duck versus quail (Fish & Schneider, 2014c; Fish et al., 2014). During neurulation, duck generate about 15% more pre-migratory neural crest cells at the levels of the midbrain and rostral hindbrain, and these are the cells that will ultimately enable them to build their long bills. Only a few stages later, duck have twice as many cells in their mandibular primordia as do quail due to species-specific variation in cell proliferation dynamics and cell cycle length.

Cell cycle length in duck mandibular mesenchyme is longer (13.5 hr) than in quail (11 hr), and this might seem counterintuitive given that duck make more cells, but when the total duration of each embryonic stage during this developmental window is considered in terms of absolute time (i.e., 45 hr for duck versus 32 hr for quail), then duck cells wind up proliferating more in total than those of quail. Therefore, by sustaining their slower intrinsic maturation rate over a longer period of time, duck implement a cellular mechanism that progressively increases jaw size during development (Fish & Schneider, 2014b; Fish et al., 2014; Schneider, 2015, 2018). In this way, duck seem to rely on time as one means to control size, which supports prior observations in birds on the correlation between innate rates of growth and body size (Ricklef & Starck, 1998; Starck, 1989; Starck & Ricklefs, 1998).

6 ORIGIN OF SPECIES-SPECIFIC PATTERN IN THE CARTILAGINOUS SKELETON

To explain more precisely how differences in the rates of development and the numbers of neural crest cells that get allocated to the mandibular primordia become species-specific determinants of size and shape, we focused on the differentiation and growth of Meckel’s cartilage in the lower jaw skeleton (Eames & Schneider, 2008). Meckel’s cartilage develops from neural crest mesenchyme into a cylindrical rod that rarely ever ossifies except in the proximal-most region (De Beer, 1937; Eames, Sharpe, & Helms, 2004; Ekanayake & Hall, 1994; Helms & Schneider, 2003; Kavumpurath & Hall, 1990; Noden, 1978b). During cartilage formation, pre-chondrogenic cells first undergo condensation and then begin overt differentiation, where they secrete extracellular matrix (Eames, de la Fuente, & Helms, 2003; Hall, 2005). There is a well-documented relationship between condensation size and skeletal size (Hall & Miyake, 1992, 1995, 2000; Miyake et al., 1996; Smith & Schneider, 1998), and from the earliest stages of chondrogenesis, we observe smaller condensations in quail relative to duck (Eames & Schneider, 2008). When we transplant presumptive neural crest from quail embryos into stage-matched duck we do so unilaterally (Figure 1d), which allows these quail donor neural crest cells to fill one side of the duck host mandible and enables us to compare the development of donor quail-derived versus host duck-derived Meckel’s cartilage in the same chimERIC quck. While the sequential stages of chondrogenesis are comparable in quail and duck, in quck chimeras, we find that quail donor neural crest cells make smaller condensations and differentiate into cartilage on a faster timetable (i.e., three stages ahead of the duck).

Accompanying these changes in quck chimeras is the premature expression of chondrogenic genes by quail donor cells relative to duck host cells on the contralateral side. For example, Sox9, which is an early molecular marker of chondrogenic condensations (Eames et al., 2003; Eames et al., 2004; Healy, Uwanogho, & Sharpe, 1996; Zhao, Eberspaecher, Lefebvre, & De Crombrugghe, 1997), and Col2a1, which is directly regulated by Sox9 (Bell et al., 1997) are both upregulated coincident with the presence of quail donor neural crest mesenchyme. Additionally, we find that FGF signaling, which operates upstream of Sox9 and chondrogenesis (Bobick, Thornhill, & Kulyk, 2007; De Crombrugghe et al., 2000; Eames et al., 2004; Govindarajan & Overbeek, 2006; Healy, Uwanogho, & Sharpe, 1999; Murakami, Kan, McKeehan, & de Crombrugghe, 2000; Petiot, Ferretti, Copp, & Chan, 2002) is also regulated by neural crest mesenchyme as evidenced by analyzing expression of the ligands Fgf4 and Fgf8, and the receptor Fgfr2. While FGF ligands are known to be expressed continuously in mandibular epithelium from the earliest embryonic stages onward (Havens, Rodgers, & Mina, 2006; Mina et al., 2002; Shigetani et al., 2000; Wall & Hogan, 1995), we find that in chimeras the receptor Fgfr2 is expressed three stages earlier by quail donor neural crest mesenchyme. If FGF signaling is blocked during this discrete temporal window when Fgfr2 becomes activated, then Meckel’s cartilage fails to form.

Ultimately, by exerting control over the timing of FGF signaling and the expression of downstream targets such as Sox9 and Col2a1,
neural crest mesenchyme likely provides cues on the molecular level that impart Meckel's cartilage with species-specific size and shape. Such a conclusion is also based on our observation that on the morphological level Meckel's cartilage displays obvious stage-specific and species-specific differences in size and shape throughout development in quail and duck, and that these differences are maintained by quail donor neural crest mesenchyme in quck chimeras (Figure 2i–n). For example, Meckel's initially forms in both duck and quail as a slightly curved cartilage that becomes more S-shaped. Shortly thereafter, Meckel's in duck remains curved while Meckel's in quail straightens out. Meckel's continues to grow in both quail and duck, but increasingly gets larger in duck. In quck chimeras, quail donor neural crest maintains its faster maturation rate within the relatively slower duck host, and the differentiation of Meckel's cartilage gets accelerated by approximately three stages on the donor side. Furthermore, the size and shape of Meckel's cartilage on the donor side becomes consistently more quail-like compared with that observed on the contralateral duck host side.

So, while surrounding endodermal and ectodermal epithelia seem to define "where" cartilage condensations form along an axis, which is most likely equivalent between quail and duck, our chimeric transplant experiments reveal that neural crest defines "when" and "what" by responding through intrinsic programs that control both stage-specific and species-specific size and shape. Significantly, this ability to keep track of stage-specific and species-specific size and shape simultaneously indicates that the neural crest cells themselves can function as a potent mechanism linking ontogeny and phylogeny. Such were the predictions made by proponents of heterochrony who argued that changes in the timing of developmental events and/or rates of growth had direct implications for the evolution of size and shape (Alberch et al., 1979; De Beer, 1930; Foster & Kaesler, 1988; Gould, 1977; Hall, 1984; Klingenberg & Spence, 1993; McKinney, 1988; Raff, 1996; Roth, 1984; Russell, 1916; Schneider, 2018). In this regard, faster-developing quail donor neural crest mesenchyme not only induces a heterochrony by altering the rates of growth in chimeras, but also the presence of these cells appears to introduce shifts in the relative onsets, cessations, or durations of molecular and cellular events, which is an additional process through which changes in time can affect size and shape (Smith, 2001–2003), especially in the context of reciprocal epithelial–mesenchymal interactions underlying skeletal evolution (Smith & Hall, 1990). Our transplants in birds with even larger disparities in growth rates like quail and emu (i.e., 17 versus 58 days from fertilization to hatching), which are separated by about seven embryonic stages during chondrogenesis, reveal that there are very few developmental constraints that prevent the host from supporting the execution of neural crest mesenchyme-dependent programs for skeletogenesis (Hall et al., 2014).

7 | ORIGIN OF SPECIES-SPECIFIC PATTERN IN THE BONY SKELETON

Akin to what we have found with cartilage, neural crest mesenchyme likewise communicates species-specific information on size and shape to bone in the jaws and facial skeleton by establishing the timing of major events during osteogenesis. In quck chimeras, quail donor neural crest mesenchyme upholds its faster timetable for maturation and autonomously executes molecular and cellular programs that promote and orchestrate each individual step of osteogenesis including the induction, proliferation, differentiation, mineralization, and remodeling of bone (Elbaa et al., 2015; Hall et al., 2014; Merrill et al., 2008). Such a capacity by neural crest mesenchyme to function as a developmental timekeeper supports earlier theoretical predictions (Alberch, 1982a; Oster & Alberch, 1982; Oster et al., 1988) about how quantitative changes to parameters within ontogenetic systems can drive morphological evolution (Schneider, 2018). For example, genetic or epigenetic modifications to "biochemical, cell–cell, or tissue interactions" (Alberch, 1985, p. 50) can in turn alter "rates of diffusion, mitotic rate, cell adhesion, etc." (Alberch, 1989, p. 27), which can then cause evolutionary changes in size and shape. Similarly, our work reveals that such quantitative changes to cellular parameters like neural crest-mediated differences between quail and duck in the number of progenitors, rate of proliferation, length of the cell cycle, and timing of differentiation leads to morphological outcomes in the bony skeleton that are species-specific.

Along these lines and as a case in point, we find that neural crest mesenchyme establishes the timing of osteogenesis in the jaw by regulating cell cycle progression (Hall et al., 2014). Seemingly, neural crest mesenchyme controls the cell cycle through stage-specific and species-specific expression of cyclin and cyclin-dependent kinase inhibitors (CKI) including p27 (cdkn1b), which is a CKI that can decrease proliferation in differentiating osteoblasts; Cyclin E (CcnE1), which is needed for G1/S phase transition; and Cyclin B1 (CcnB1), which is essential for G2/M phase transition (Coats, Flanagan, Nourse, & Roberts, 1996; Drissi et al., 1999; Vavitz & Zipursky, 1997). We find species-specific differences in the expression and post-translational processing of these cell cycle regulators, which we predict could permit birds like quail to shorten their period of mesenchymal proliferation and lead to faster-differentiating and smaller beak skeletons. For example, in quail and on the donor side of quck, we find that p27 is up-regulated relative to that observed in duck. Previous experiments have demonstrated that p27 is associated with size, including p27-deficient mice, which are much larger than their wild-type littermates yet have no obvious defects in their skeletons (Drissi et al., 1999). Likewise, the frontonasal process of duck has lower p27 levels than that observed in chick (Powder et al., 2012), and furthermore the mandibular primordia shows tissue-specific post-translational regulation of p27, like what has been reported in other systems (Hirano et al., 2001; Zhang, Bergamaschi, Jin, & Lu, 2005). Therefore, changing p27 levels may affect tissue- and species-specific size and/or total growth. This direct connection between the regulation of cell cycle progression and the timing of events throughout bone development offers a mechanism through which neural crest mesenchyme might be able to generate changes in skeletal size and shape during evolution.

The potential for such a mechanism is further supported by experiments in which we can mimic the results observed in quck chimeras by prematurely inducing cell cycle exit. In this scenario, we find that the molecular program for osteogenesis becomes accelerated (Hall et al., 2014). Specifically, we observe early and elevated expression of genes such as Runx2, which is known to be a “master
regulator" of bone formation that can direct osteoblast differentiation, influence skeletal size, and control the timing of mineralization (Ducy et al., 1998; Ducy, Zhang, Geoffroy, Ridall, & Karsenty, 1997; Eames et al., 2004; Galindo et al., 2005; Komori et al., 1997; Maeno et al., 2011; Otto et al., 1997; Pratap et al., 2003; Thomas et al., 2004). Neuronal crest mesenchyme in the mandibular primordia normally expresses Runx2 during a tightly controlled temporal window and at well-defined levels (Eames et al., 2004; Merrill et al., 2008), but by over-expressing Runx2 prematurely and at higher levels in chick embryos, we can markedly reduce the size of the beak skeleton (Hall et al., 2014). This in effect, reflects the relationship normally observed between endogenous Runx2 levels and species-specific beak size. In fact, when the quail jaw skeleton begins to mineralize, its Runx2 levels are more than twice that found in duck. Along these lines, other studies have hypothesized that there is a mechanistic link between predicted differential levels of Runx2 expression (based on ratios of tandem repeats in DNA) and the length of the face among dogs and other mammals (Fondon and Garner, 2004; Pointer et al., 2012; Sears, Goswami, Flynn, & Niswander, 2007).

That neural crest mesenchyme regulates the timing and levels of Runx2 expression, and that this in turn has a direct effect on skeletal size, fulfills predictions made more than 75 years ago by embryologists such as Huxley (1932) and Goldschmidt (1938, 1940) with regard to the existence of genes that establish the time and rate of development (Schneider, 2018). Along similar lines, De Beer (1954) argued that, “by acting at different rates, the genes can alter the time at which certain structures appear” (p. 20). Data from in vitro experiments also help explain how Runx2 could function in this capacity whereby Runx2 expression both depends upon and regulates cell cycle progression through mechanisms such as the repression of RNA synthesis and the up-regulation of p27 (Galindo et al., 2005; Pratap et al., 2003; Thomas et al., 2004; Young et al., 2007). Collectively, these observations indicate that neural crest mesenchyme establishes species-specific size and shape in the bony skeleton by mediating the timing of the transition from proliferation to differentiation and by modulating the expression levels of osteogenic transcription factors such as Runx2.

Neural crest mesenchyme also appears to exert control over species-specific size and shape during osteogenesis upstream of Runx2 by governing the temporal and spatial expression of members and targets of the BMP pathway (Merrill et al., 2008). BMP ligands can induce bone formation both embryonically (Kingsley et al., 1992; Luo et al., 1995; Solloway et al., 1998) and postnatally (Urist, 1965; Wang et al., 1990; Wozney et al., 1988). During jaw development, Bmp2, Bmp4, and Bmp7, as well as their receptors (Bmpr1a, Bmpr1b, and Alk2) are expressed in mandibular mesenchyme and/or epithelium (Ashique et al., 2002a; Bennett, Hunt, & Thorogood, 1995; Francis-West, Tatla, & Brickle, 1994; Wall & Hogan, 1995), and they play critical roles during osteogenesis (Ashique et al., 2002b; Francis-West et al., 1998; Wang et al., 1998). For example, BMP4 helps neural crest mesenchyme differentiate into bone (Abzhanov, Rodda, McMahon, & Tabin, 2007) and the lower jaw fails to form when Bmp4 is conditionally eliminated from mandibular epithelium (Liu et al., 2005). BMP signaling regulates osteogenesis via a highly conserved pathway (Derynck, Piek, Schneider, Choy, & Alliston, 2008; Heldin, Miyazono, & ten Dijke, 1997; Kawabata, Imamura, & Miyazono, 1998; Massague & Wotton, 2000) involving Smad activation, which in turn affects Runx2 expression (Ducy, 2000; Ducy et al., 1997; Kang, Alliston, Delston, & Derynck, 2005; Karsenty et al., 1999; Komori et al., 1997) and mandibular osteogenesis (Otto et al., 1997). Moreover, physical interactions between SMAD proteins and Runx2 drive osteoblast-specific gene expression (Alliston, Choy, Ducy, Karsenty, & Derynck, 2001; Ito et al., 2002; Lee et al., 2000).

Other targets of BMP signaling including Msx1 (Tribulo, Aybar, Nguyen, Mullins, & Mayor, 2003) play a role during the epithelial-mesenchymal interactions of the mandible (Beil & Maas, 1998; Chen & Struhl, 1996; Han et al., 2007), are neural crest-mediated (Schneider & Helms, 2003), and affect bone formation (Royaal et al., 2010; Satokata & Maas, 1994).

As part of its osteo-inductive role, BMP signaling likely shapes the avian beak by creating domains of differential growth within the mesenchyme. For instance, distinct domains of Bmp4 expression in the frontonasal primordium contribute to beak width and depth among birds including Darwin’s finches, cockatiels, chicks, and ducks (Abzhanov et al., 2004; Schneider, 2007; Wu et al., 2004, 2006). Likewise, over-expressing Bmp4 in cichlid fish that usually form elongated jaws, shortens and widens the jaw and in effect phenocopies features that are coupled with the evolution of distinct feeding strategies (Albertson, Streelman, Kocher, & Yelick, 2005). This salient ability of neural crest mesenchyme to control the timing of osteogenesis by autonomously executing molecular programs involving BMP signaling as well as transcriptional targets such as Msx1 and Runx2, likely serves as a key developmental mechanism facilitating the evolution of species-specific size and shape in the craniofacial skeleton.

8 | ORIGIN OF SPECIES-SPECIFIC PATTERN DURING BONE RESORPTION

While much of the work we have performed has demonstrated that neural crest mesenchyme conveys species-specific size and shape to the craniofacial skeleton by regulating molecular and cellular programs for the induction and deposition of cartilage and bone, we have also discovered that a previously underappreciated but potentially just as important mechanism affecting species-specific shape and size lies in the ability of neural crest mesenchyme to direct the process of bone resorption (Elba et al., 2015; Schneider, 2015). Usually, bone resorption is tied to bone deposition as a metabolic function for maintaining homeostasis in the adult skeleton (Buckwalter, Glimcher, Cooper, & Recker, 1996; Filvaroff & Derynck, 1998; Hall, 2005; Nguyen, Tang, Nguyen, & Alliston, 2013; O’Brien et al., 2008; Teitelbaum, 2000; Teitelbaum, Tondravi, & Ross, 1997). In contrast, little is known about the role of resorption during skeletal patterning in embryos, except for a few hypotheses about the effects of differential fields of bone resorption on the size and shape of the developing human jaw skeleton (Enlow, Moyers, & Merow, 1975; Moore, 1981; Raldisani & Klarkowski, 2001; Raldisani, Renz, Lajvardi, & Schneider, 2004) and recent work on the remodeling of Meckel’s cartilage by chondroclasts in mammals (Anthwal, Urban, Luo, Sears, & Tucker, 2017).
When we assay for molecular and enzymatic markers of bone resorption we observe significantly higher levels and distinct spatial domains in quail versus duck that correlate with species-specific differences in beak size and shape. There are two populations of cells that resorb bone in the craniofacial skeleton. Osteoclasts arise from the mesodermal hematopoietic lineage (Couly, Coltey, Eichmann, & Le Douarin, 1995; Couly et al., 1992; Jotereau & Le Douarin, 1978; Kahn et al., 2009), and osteocytes (Akił et al., 2014; Belanger, 1969; Fowler et al., 2017; Jauregui et al., 2016; O’Brien et al., 2008; Qin et al., 2012; Tang, Herber, Ho, & Alliston, 2012; Xiong & O’Brien, 2012; Xiong et al., 2014) are derived entirely from neural crest mesenchyme (Helms & Schneider, 2003; Le Lièvre, 1978; Noden, 1978b). Therefore, in our quail-duck chimeras, all osteoclasts form exclusively from the host mesoderm whereas all osteocytes come from the donor neural crest.

Osteoclasts and osteocytes secrete tartrate-resistant acid phosphatase (TRAP) when they are actively resoring bone (Minkin, 1982; Qin et al., 2012; Tang et al., 2012). Also, osteoclasts express Matrix Metalloproteinase 9 (Mmp9) (Engsig et al., 2000; Reponen, Sahilberg, Munaut, Thesleff, & Tryggvason, 1994) and osteocytes express Mmp13 (Behonick et al., 2007; Johansson et al., 1997; Sasano et al., 2002). Accordingly, in the lower jaw of chimeric quck, Mmp9 is expressed by duck host-derived osteoclasts while Mmp13 is expressed by quail donor-derived osteocytes. We find that control quail express substantially higher levels of TRAP, Mmp9, and Mmp13 than do duck, suggesting that increased resorption may relate to shorter beaks (Ealba et al., 2015). Similarly, chimeric quck have greatly elevated TRAP, Mmp9, and Mmp13 expression in association with the donor-mediated transformation into quail-like beaks, which implies that quail donor neural crest mesenchyme executes an autonomous species-specific program that controls bone resorption by its own derivatives (i.e., osteoclasts) as well as by those of the duck host (i.e., osteoclasts). This provides another neural crest-dependent mechanism that contributes to the shorter beaks of quail and chimeric quck.

In support of this conclusion, we find that when we experimentally apply small molecules, pharmacologic agents, or recombinant proteins to inhibit resorption we can lengthen the beak, whereas if we activate resorption we can shorten the beak.

By extension then, our work reveals that beak size in birds is inversely proportional to levels of bone resorption, and that such levels are established by neural crest mesenchyme. Prior work on Darwin’s finches and other species, have correspondingly argued that the calcium binding protein Calmodulin is a key determinant of beak length (Abzhanov et al., 2006; Gunter, Koppermann, & Meyer, 2014; Schneider, 2007). Quite interestingly, Calmodulin is known to regulate osteoclasts and osteocytes (Choi, Ann, et al., 2013; Choi, Choi, Oh, & Lee, 2013; Seales, Micoli, & McDonald, 2006; Zayzafou, 2006), calcium signaling is important for bone resorption (Hwang & Putney, 2011; Kajiya, 2012; Xia & Ferrier, 1996; Xiong et al., 2014), and this pathway can affect jaw size (Gunter et al., 2014; Parsons & Albertson, 2009). Thus, taken together, all of these studies imply that bone resorption may function like a rheostat during skeletal evolution, and in this capacity might be especially tuned to the availability of dietary calcium, to the effects of calcium-dependent hormones, and to gradients of calcium signaling within the beak primordia (Schneider, 2007, 2018). Such spatial and temporal regulation of resorption by neural crest mesenchyme likely acts as a determinant of species-specific size and shape by creating local zones of resorption in quail versus duck that more-or-less sculpt the bone and inhibit or promote directional growth.

Overall, we have discovered that neural crest mesenchyme wields precise spatial and temporal control over each step of osteogenesis including the induction, differentiation, deposition, mineralization, and resorption of bone (Ealba et al., 2015; Eames & Schneider, 2008; Hall et al., 2014; Merrill et al., 2008; Schneider & Helms, 2003). This control appears to be integrated and implemented on multiple interacting genetic and epigenetic levels (Alberch, 1982a) such that neural crest can orchestrate species-specific programs for skeletal size and shape throughout development and serve as a source for morphological variation in the craniofacial complex during evolution. Most likely, the mechanisms that distinguish the species-specific programs of quail from those of duck are multifactorial and based on intrinsic and emergent differences in genome organization, cis-regulation of individual genes, epigenetic activities of non-coding RNA at the transcriptional and post-transcriptional level, connectivity at nodes within gene regulatory networks, biochemical interactions among gene products (e.g., enzymes and other proteins), post-translational modification of proteins, diffusion-reaction gradients and thresholds that affect induc- tion and developmental potential, properties and movements of cells, and/or physical and signaling interactions among tissues (Schneider, 2018). Changes at any of these hierarchical levels of organization during development could undoubtedly be a means to affect species-specific morphology. By investigating such changes in quail versus duck we aspire to rise to the challenge set forth by Alberch et al. (1979) when they expressed their hope that their “attempts to construct a quantitative theory will stimulate others to delve more deeply below the level of pure phenonomology and come to grips with the central issue underlying evolutionary diversification of size and shape—that is, the morphogenetic unfolding of genetic programs in ontogeny and their alteration in the course of phyletic evolution” (p. 297).

9 | ORIGIN OF SPECIES-SPECIFIC PATTERN IN THE JAW MUCULATURE

In addition to cartilage and bone, cranial neural crest mesenchyme also produces skeletal and muscle connective tissues such as tendons, ligaments, fascia, and epi- and endomysia (Couly et al., 1993; Köntges & Lumsden, 1996; Le Lièvre & Le Douarin, 1975; Noden, 1978b, 1983; Noden & Schneider, 2006). Head and jaw muscles however, form from mesodermal mesenchyme (Couly et al., 1992; Evans & Noden, 2006; Noden, 1983; Noden & Francis-West, 2006; Noden & Trainor, 2005; Scaal & Marcelle, 2018; Wachtler & Jacob, 1986). Given these differences in embryonic origin, the quail-duck chimeric system provides a means to examine the extent to which donor neural crest mesenchyme regulates species-specific pattern in host muscle (Fish & Schneider, 2014b; Solem et al., 2011; Tokita & Schneider, 2009). A broad range of prior investigations have revealed that cranial neural crest mesenchyme plays a critical role during muscle
development. In particular, the early migration, differentiation, and spatial patterning of myogenic mesenchyme in the head relies on interactions with surrounding muscle connective tissues (Boroue & Noden, 2004; Ericsson, Cerny, Falck, & Olsson, 2004; Francis-West et al., 2003; Grammatopoulos et al., 2000; Grenier, Teillet, Grifone, Kelly, & Duprez, 2009; Hall, 1950; Knight, Mebus, & Roehl, 2008; Knight & Schilling, 2006; Köntges & Lumsden, 1996; McGurk et al., 2017; Noden, 1983, 1986a, 1988; Noden, Marcucio, Borycki, & Emerson, 1999; Noden & Schneider, 2006; Noden & Trainor, 2005; Olsson, Falck, Lopez, Cobb, & Hanken, 2001; Pasqualetti et al., 2000; Rinon et al., 2007; Schilling et al., 1996; Schnorrer & Dickson, 2004; Subramanian & Schilling, 2015; Sugii et al., 2017; Tokita, Nakayama, Schneider, & Agata, 2013; Trainor & Krumlauf, 2000; Trainor, Sobieszczuk, Wilkinson, & Krumlauf, 2002; Tzahor et al., 2003).

With regard to the species-specific patterning of the muscles, a clear example of the effects of neural crest mesenchyme can be seen in the resultant jaw complex of quail-duck chimeras. Quail and duck have highly specialized jaw morphologies associated with their species-specific modes of feeding. Quail use their sharp, pointed beaks like forceps to peck at seed on the ground whereas duck use a suction-pump mechanism and apply leverage across their long, broad bills to strain water and sediment. Such differences in feeding behavior are mirrored in the size, shape, and attachment sites of their jaw muscles as well as in their jaw kinetics and mechanics (Bout & Zweers, 2001; Dawson, Metzger, Baier, & Brainerd, 2011; Fisher, 1955; Soni, 1979; Zweers, 1974; Zweers, Gerritsen, & Kraneburg-Voogd, 1977; Zweers, Kunz, & Mos, 1977) (Figure 3a–d). In quail-duck chimeras we find that quail donor neural crest mesenchyme imparts quail-like pattern on the duck host mesoderm-derived jaw muscles (Solem et al., 2011; Tokita & Schneider, 2009). These transformations are not only species-specific but also stage-specific, in that the muscle anatomy on the donor side is more like that found in control quail three stages later. For example, in duck, the mandibular adductor muscle inserts on the lateral side of the mandible (Zweers, 1974; Zweers, Kunz, et al., 1977), whereas in quail, the same muscle inserts on the dorsal surface of the mandible (Baumel, 1993; Van den Heuvel, 1992). In quck chimeras, these species-specific differences in the shape, orientation, and insertion point of the mandibular adductor muscle are patterned by neural crest mesenchyme. In particular, we find that quail donor neural crest mesenchyme is distributed throughout the skeletal and muscular connective tissues that surround the developing host muscle precursors and causes the duck host jaw muscles to elongate rostrally and attach dorsally as in quail (Solem et al., 2011; Tokita & Schneider, 2009; Woronowicz et al., 2018) (Figure 3e–j).

Preceding these dramatic morphological transformations are changes to the spatial and temporal patterns of gene expression for muscle connective tissue markers such as Tcf4, which is a transcription factor that functions downstream of the WNT pathway, and which plays an essential role during muscle development (Anakwe et al., 2003; Bonafede, Kohler, Rodriguez-Niedenfuhr, & Brand-Saberi, 2006; Mathew et al., 2011; Miller et al., 2007) including ordaining the spatial pattern of limb muscles (Kardon, Harfe, & Tabin, 2003). Another transcription factor, Scleraxis (Scx), which is expressed by and required for the differentiation of tendon and ligament progenitors in the trunk and head (Berthet et al., 2013; Blizt, Sharir, Akiyama, & Zelzer, 2013; Blizt et al., 2009; Brent, Braun, & Tabin, 2005; Cserjesi et al., 1995; Grenier et al., 2009; Murchison et al., 2007; Pryce, Brent, Murchison, Tabin, & Schweitzer, 2007; Schweitzer et al., 2001; Shukunami, Takimoto, Oro, & Hiraki, 2006), is also up-regulated on the donor side of quck chimeras in quail-like patterns. Thus, these neural crest-mediated changes in gene expression appear to direct the species-specific shape and attachment sites of the jaw muscles. This in turn, alters the functional morphology and the associated mechanical force environment such that the duck host side of quck chimeras induces Sox9 expression and a robust secondary cartilage at the insertion of the mandibular adductor muscle on the coronoid process of the mandible, whereas the quail donor side fails to express Sox9 or form a secondary cartilage just like in control quail (Solem et al., 2011; Woronowicz et al., 2018) (Figure 3k–n).

Interestingly, donor neural crest mesenchyme does not seem to alter the early programs for host myogenic specification or muscle differentiation, which based on our expression analyses of early muscle markers and structural proteins continue to follow the timetable of the host (Tokita & Schneider, 2009). Such a result is not entirely surprising given that muscle is an ancient mesodermal lineage that evolved long before the appearance of the cranial neural crest and therefore, likely executes aspects of its own developmental program rather autonomously. This also appears to be the case for the mesodermally-derived blood vessels of the host, which are similarly unaffected in chimeras (Hall et al., 2014). However, this situation is quite unlike what we have observed for the donor-derived programs for cartilage, bone, and tendon, and the host-derived programs for epidermis (i.e., feathers and egg teeth) and osteoclasts, which in chimeras all follow in lockstep with the quail donor timetable and become accelerated by three stages (Ealba et al., 2015; Eames & Schneider, 2005, Eames & Schneider, 2008; Hall et al., 2014; Merrill et al., 2008; Schneider & Helms, 2003).

In sum, neural-crest mesenchyme and its muscle connective tissue derivatives transmit species-specific patterning information to craniofacial muscles by executing autonomous molecular programs and by dominating interactions with their partners from the mesoderm. Such mechanistic insights help explain how skeletal and muscular components in the jaw complex have so intimately co-evolved as species radiate into new niches and their mouthparts become adapted in various ways. This can be seen clearly in birds such as parrots, where the number and organization of jaw muscles have been extremely modified, and most likely in close association with changes to neural crest (Tokita, 2004, 2006; Tokita, Kiyoshi, & Armstrong, 2007; Tokita et al., 2013; Zusi, 1993). The fact that neural crest mesenchyme establishes a direct relationship between skeletal anatomy, muscle architecture, and feeding mechanics suggests that the capability of a given species to modify its jaw complex rapidly during evolution, which is critical to accommodate novel ecological conditions, resides in the cranial neural crest. Thus, the neural crest has played a leading role in dictating species-specific pattern and in directing the structural and functional integration of the craniofacial complex during the course of vertebrate evolution.
FIGURE 3  (a) Adult quail and (b) duck heads in lateral view showing the mandibular adductor muscles that close the jaw (yellow dashed lines). The duck mandibular adductor inserts more laterally and proximally, and integrates into a pronounced coronoid process along the side of the lower jaw (black arrow) whereas the quail mandibular adductor inserts more dorsally and distally. Modified from Tokita and Schneider (2009). (c) Lateral view of cleared and stained quail and (d) duck embryos at stage 41. Cartilage is blue and bone is red. In duck, the coronoid process forms as a secondary cartilage (white arrow) on the lateral side of the surangular bone along the lower jaw skeleton. A corresponding cartilage is absent in quail (white asterisk). (e) In quck chimeras, jaw muscles come from the duck host whereas skeletal and connective tissues come from quail donor neural crest. Jaw anatomy on the donor side is transformed to something more like that found in quail. The mandibular adductor is narrower, inserts dorsally along the surangular, and as in quail, does not contain secondary cartilage. (f) In contrast, on the host side of quck, the mandibular adductor muscle is broader and inserts laterally on the surangular bone, and secondary cartilage forms within the insertion (white arrow) like that normally observed in duck. (g) Trichrome-stained section of duck in lateral view showing the mandibular adductor muscle at its insertion (black arrow and stained purple), which is wide and triangular shaped along the surangular bone (stained blue). (h) On the host side of quck, the insertion looks the same as in duck whereas (i) on the donor side of quck (white asterisk) and in (j) quail the insertion is relatively thin. (k) Coincident with the eventual formation of secondary cartilage in duck but not quail, the chondrogenic transcription factor Sox9 is expressed highly in the insertion (white arrow) of duck and (l) on the host side of quck, but not in the insertion (m) on the donor side of quck (white asterisk) or (n) in quail. Modified from Solem et al. (2011)
10 | CONCLUSION

The vertebrate craniofacial complex displays tremendous conservation in its anatomical organization but remarkable diversity in its species-specific size and shape. Such dualism mirrors the need for the craniofacial complex to satisfy essential requirements for survival like feeding, breathing, and sensing, yet simultaneously generate enough morphological variation to allow for adaptive evolution. Conspicuously, much of the evolutionary diversity in the craniofacial complex has appeared in those structures derived from the cranial neural crest, suggesting a high degree of plasticity (Eames & Schneider, 2005; Fish & Schneider, 2014b; Gans & Northcutt, 1983; Hanken & Gross, 2005; Jheon & Schneider, 2009; Le Douarin et al., 2004; Noden & Schneider, 2006; Northcutt, 2005; Schlosser & Wagner, 2004; Schneider, 1999, 2005, 2015; Trainor et al., 2003; West-Eberhard, 1989, 2003; Young et al., 2014).

To this point, one might ask, what endows the cranial neural crest with both the plasticity to drive evolutionary diversification and the regulatory abilities to put them near the top of hierarchies in developmental programs for species-specific pattern? Contributing factors may include gene duplication events, which are believed to have capacitated the evolution of neural crest development via co-option and novel gene function (Green & Bronner, 2013; Meulemans & Bronner-Fraser, 2005). Similarly, results from transcriptional profiling studies point to novel signaling pathways and suites of transcription factors that are enriched in sub-populations of neural crest (Lumb, Buckberry, Secker, Lawrence, & Schwarz, 2017; Simeos-Costa & Bronner, 2016; Simeos-Costa, Tan-Cabugao, Antoshechkin, Sauka-Spengler, & Bronner, 2014). Moreover, given that cranial neural crest derivatives participate deeply in the development and patterning of multiple systems including the nervous, neuroendocrine, integumentary, and skeletal, regulatory changes to the neural crest can be a major source of simultaneous evolutionary transformations in behavior, pigmentation, as well as the size and shape of cartilage and bone in the face (Lord et al., 2016; Sanchez-Villagra et al., 2016; Schneider, 2005, 2018; Singh et al., 2017; Wilkins et al., 2014).

Without a doubt, data from a wide variety of experimental systems and strategies performed in diverse vertebrate taxa, demonstrate that neural crest mesenchyme controls species-specific pattern. Work from our lab takes this conclusion one step further and reveals that neural crest does so by autonomously executing molecular and cellular programs for making neural crest-derived structures, as well as by governing the required interactions with adjacent tissues (e.g., ectodermal epithelia and mesodermal mesenchyme). Furthermore, the precise origin of species-specific pattern is rooted in the fact that epithelia are generally permissive and supply generic anatomical information (e.g., “form a lower jaw”) while neural crest mesenchyme contains instructive information for size and shape (e.g., “form a quail-like lower jaw” versus “form a duck-like lower jaw”). In other words, the list of parts is more or less the same but the species-specific differences that arise during the construction process appear to stem from where, when, and how long neural crest mesenchyme autonomously activates and executes intrinsic molecular programs including the expression of receptors that allow for signal transduction to begin and end, as well as a variety of transcription factors that modulate gene regulatory networks. Ultimately, the developmental fate of each species is determined by the differential unfurling of each genome in three dimensions as a function of absolute and/or relative time (e.g., cell cycle dynamics and maturation rates).

Most significantly, the propensity of neural crest mesenchyme to keep track concurrently of stage-specific and species-specific time, size, and shape provides a potent mechanism linking ontogeny and phylogeny in the integumentary and musculoskeletal systems, both of which have been critical to the success of vertebrates. Such findings about the integration of these systems vis-à-vis the cranial neural crest also reveal the many ways development can play a “generative and regulatory” role in the evolution of species-specific pattern (Alberch, 1982b), and they help substantiate heterochrony as a viable developmental mechanism whereby species-specific transformations in size and shape can come about via changes in the timing of developmental events (Alberch et al., 1979; De Beer, 1930; Fish & Schneider, 2014b; Hall, 1984; Schneider, 2018; Smith, 2003).

In this framework, a major remaining question for future research involves identifying on a much larger scale (i.e., systems level) where, when, and how variation in the molecular and cellular programs that are directed by the neural crest leads to species-specific changes in size and shape. Addressing this question has important implications for understanding both evolution and the etiologies of craniofacial birth defects (Schneider, 2015). Furthermore, heterochrony may be an oversimplification of the many processes at work and instead a more multidimensional strategy that accounts for the effects of complex changes in facets such as the levels and spatial distribution of gene expression over developmental time (Depew & Simpson, 2006) may be necessary. Additional approaches that incorporate genome-wide differences in the regulation of neural crest-mediated programs among divergent taxa, have great potential to elucidate these issues (Betancur, Bronner-Fraser, & Sauka-Spengler, 2010; Long, Prescott, & Wysocka, 2016; Nikitina et al., 2008; Prescott et al., 2015; Rebez & Tsiantis, 2017; Sauka-Spengler & Bronner-Fraser, 2008; Sauka-Spengler et al., 2007; Trinh et al., 2017; Williams et al., 2018). One can only imagine what the next 150 years of neural crest biology will uncover.

ACKNOWLEDGMENTS

I thank my collaborators and trainees whose work over the years forms the basis for much of what I have reviewed here (I have tried to cite them whenever possible). I am also very grateful to my long-time mentor Drew Noden, who took me under his wing and got me hooked on crest while I was a fledgling graduate student more than two decades ago.

ORCID

Richard A. Schneider http://orcid.org/0000-0002-2626-3111

REFERENCES

Abranyan, J., Leung, K. J., & Richman, J. M. (2014). Divergent palate morphology in turtles and birds correlates with differences in proliferation
and BMP2 expression during embryonic development. *Journal of Experimental Zoology. Part B, Molecular and Developmental Evolution*, 322, 73–85.

Abrahamyan, J., & Richman, J. M. (2018). Craniofacial development: Discoveries made in the chicken embryo. *The International Journal of Developmental Biology*, 62, 97–107.

Abzhanov, A., Kuo, W. P., Hartmann, C., Grant, B. R., Grant, P. R., & Tabin, C. J. (2006). The calmodulin pathway and evolution of elongated beak morphology in Darwin’s finches. *Nature*, 442, 563–567.

Abzhanov, A., Protas, M., Grant, B. R., Grant, P. R., & Tabin, C. J. (2004). Bmp4 and morphological variation of beaks in Darwin’s finches. *Science* (New York, N.Y.), 305, 1462–1465.

Abzhanov, A., Rodda, S. J., McMahon, A. P., & Tabin, C. J. (2007). Regulation of skeletogenic differentiation in cranial dermal bone. *Development (Cambridge, England)*, 134, 3133–3144.

Abzhanov, A., & Tabin, C. J. (2004). Shh and Fgf8 act synergistically to drive cartilage outgrowth during cranial development. *Developmental Biology*, 273, 134–148.

Adams, A. E. (1931). Some effects of removal of endoderm from the mouth region of early Amblystoma punctatum embryos. *Journal of Experimental Zoology*, 58, 147–163.

Ahlgren, S. C., & Bronner-Fraser, M. (1999). Inhibition of sonic hedgehog signaling in vivo results in craniofacial neural crest cell death. *Current Biology*; Ch, 9, 1304–1314.

Ainsworth, S. J., Stanley, R. L., & Evans, D. J. (2010). Developmental stages of the Japanese quail. *Journal of Anatomy*, 216, 3–15.

Akil, O., Hall-Glenn, F., Chang, J., Li, A., Chang, W., Lustig, L. R., … Hsiao, E. C. (2014). Disrupted bone remodeling leads to cochlear outgrowth and hearing loss in a mouse model of fibrous dysplasia. *PLoS One*, 9, e94989.

Alberch, P. (1985). Problems with the interpretation of developmental sequences. *Systematic Zoology*, 34, 46–58.

Alberch, P. (1989). The logic of monsters: Evidence for internal constraint in development and evolution. *Geobios*, 22, 21–57.

Alberch, P., Gould, S. J., Oster, G. F., & Wake, D. B. (1979). Size and shape in ontogeny and phylogeny. *Paleobiology*, 5, 296–317.

Albertson, R. C., Streelman, J. T., Kocher, T. D., & Yelick, P. C. (2005). Integration and evolution of the cichlid mandible: The molecular basis of alternate feeding strategies. *Proceedings of the National Academy of Sciences of the United States of America*, 102, 16287–16292.

Alliston, T., Choy, L., Ducy, P., Karsenty, G., & Derynck, R. (2001). TGF-beta-induced repression of CBFA1 by Smad3 decreases cbfa1 and osteocalcin expression and inhibits osteoblast differentiation. *The Embo Journal*, 20, 2254–2272.

Alvarado-Mallart, R. M. (2005). The chick/quail transplantation model: Dissection made in the chicken embryo. *Anatomy and Embryology*, 220, 1–15.

Anwar, M., Tambalo, M., Ranganathan, R., Grocott, T., & Streit, A. (2017). A gene network regulated by FGF signalling during ear development. *Scientific Reports*, 7, 6162.

Arthur, W. (2006). D’Arcy Thompson and the theory of transformations. *Nature Reviews. Genetics*, 7, 401–406.

Ashique, A. M., Fu, K., & Richman, J. M. (2002a). Endogenous bone morphogenetic proteins regulate outgrowth and epithelial survival during avian limb fusion. *Development*, 129, 4647–4660.

Ashique, A. M., Fu, K., & Richman, J. M. (2002b). Signalling via type IA and type IB bone morphogenetic protein receptors (BMPR) regulates intramembranous bone formation, chondrogenesis and feather formation in the chicken embryo. *International Journal of Developmental Biology*, 46, 243–253.

Atchley, W. R., Rutledge, J. J., & Cowley, D. E. (1981). Genetic components of size and shape. II. Multivariate covariance patterns in the rat and mouse skull. *Evolution; International Journal of Organic Evolution*, 35, 1037–1055.

Atit, R., Conlon, R. A., & Niswander, L. (2003). EGF signaling patterns the feather array by promoting the interbud fate. *Developmental Cell*, 4, 231–240.

Baker, C. V., & Bronner-Fraser, M. (2001). Vertebrate cranial placodes 1. Embryonic induction. *Developmental Biology*, 232, 1–61.

Baker, C. V., Bronner-Fraser, M., Le Douarin, N. M., & Teillet, M. A. (1997). Early- and late-migrating cranial neural crest cell populations have equivalent developmental potential in vivo. *Development (Cambridge, England)*, 124, 3077–3087.

Baker, C. V., Stark, M. R., Marcelle, C., & Bronner-Fraser, M. (1999). Competition, specification and induction of PAX-3 in the trigeminal placode. *Development (Cambridge, England)*, 126, 147–156.

Balaban, E. (1997). Changes in multiple brain regions underlie species differences in a complex, congenital behavior. *Proceedings of the National Academy of Sciences of the United States of America*, 94, 2001–2006.

Balaban, E., Teillet, M. A., & Le Douarin, N. (1988). Application of the quail-chick chimera system to the study of brain development and behavior. *Science*, 241, 1339–1342.

Balczerski, B., Zakaria, S., Tucker, A. S., Borycki, A. G., Koyama, E., Pacifici, M., & Francis-West, P. (2012). Distinct spatiotemporal roles of hedgehog signalling during chick and mouse cranial base and axial skeleton development. *Developmental Biology*, 371, 203–214.

Balling, R., Mutter, G., Gruss, P., & Kessel, M. (1989). Craniofacial abnormalities induced by ectopic expression of the homeobox gene Hox-1.1 in transgenic mice. *Cell*, 58, 337–347.

Bancroft, M., & Bellairs, R. (1977). Placodes of the chick embryo studied by *SEM. Anatomy and Embryology*, 151, 97–108.

Barlow, A. J., & Francis-West, P. H. (1997). Ectopic application of recombinant BMP-2 and BMP-4 can change patterning of developing chick facial primordia. *Development (Cambridge, England)*, 124, 391–398.

Baumel, J. J. (1993). *Handbook of avian anatomy: Nomina anatomica avium*. Cambridge, MA: Nuttall Ornithological Club.

Bee, J., & Thorogood, P. (1980). The role of tissue interactions in the skeletogenic differentiation of avian neural crest cells. *Developmental Biology*, 78, 47–66.

Behonick, D. J., Xing, Z., Lieu, S., Buckley, J. M., Lotz, J. C., Marcucio, R. S., … Colnot, C. (2007). Role of matrix metalloproteinase 13 in both endochondral and intramembranous ossification during skeletal regeneration. *PLoS One*, 2, e1150.

Beil, M., & Maas, R. (1998). FGFRs and BMP4 induce both Msx1-independent and Msx2-dependent signaling pathways in early tooth development. *Development (Cambridge, England)*, 125, 4325–4333.

Belanger, L. F. (1969). Osteocytic osteolysis. *Calcified Tissue Research*, 7, 151–158.

Belle, J., & Thorogood, P. (1980). The role of tissue interactions in the skeletogenic differentiation of avian neural crest cells. *Developmental Biology*, 78, 47–66.

Belanger, L. F. (1969). Osteocytic osteolysis. *Calcified Tissue Research*, 7, 151–158.

Bell, D. M., Leung, K. K., Wheatley, S. C., Ng, L. J., Zhou, S., Ling, K. W., … Streit, A. (2003). Wnt signalling regulates myogenic differentiation in the developing avian wing. *Development (Cambridge, England)*, 130, 3503–3514.

Anderson, B. G., & Busch, H. L. (1941). Allometry in normal and regenerating antennal segments in daphnia. *Biological Bulletin*, 81, 119–126.

Anderson, R. M., Lawrence, A. R., Stottrmann, R. W., Bachiller, D., & Klingensmith, J. (2002). Chordin and noggin promote organizing centers of forebrain development in the mouse. *Development (Cambridge, England)*, 129, 4975–4987.

Andres, G. (1949). Untersuchungen an Chimären von Triton und Bomina. *Genetica*, 24, 387–534.

Anthwal, N., Urban, D. J., Luo, Z. X., Sears, K. E., & Tucker, A. S. (2017). Meckel’s cartilage breakdown offers clues to mammalian middle ear evolution. *Nature Ecology & Evolution*, 1, 93.
Clouthier, D. E., Williams, S. C., Yanagisawa, H., Wieduweit, M., Richardson, J. A., & Yanagisawa, M. (2000). Signaling pathways crucial for craniofacial development revealed by endothelin-A receptor-deficient mice. Developmental Biology, 217, 10–24.

Coats, S., Flanagan, W. M., Nourse, J., & Roberts, J. M. (1996). Requirement of p27Kip1 for restriction point control of the fibroblast cell cycle. Science (New York,N.Y.), 272, 877–880.

Cobos, I., Shimamura, K., Rubenstein, J. L., Martinez, S., & Puelles, L. (2001). Fate map of the avian anterior forebrain at the four-somite stage, based on the analysis of quail-chick chimeras. Developmental Biology, 239, 46–67.

Cohen, M. A., Wert, K. J., Goldmann, J., Markoukli, S., Buganim, Y., Fu, D., & Jaenisch, R. (2016). Human neural crest cells contribute to coat pigmentation in interspecies chimeras after in utero injection into mouse embryos. Proceedings of the National Academy of Sciences of the United States of America, 113, 1570–1575.

Copenhaver, W. M. (1930). Results of heteroplastic transplantation of anterior and posterior parts of the heart rudiment in Amblystoma embryos. Journal of Experimental Zoology, 55, 293–318.

Coppler, L., & Coppinger, R. P. (1982). Livestock-guarding dogs that wear sheep’s clothing. Smithsonian, 15, 64–72.

Cooper, R. P., & Schneider, R. A. (1995). Evolution of working dogs. In J. Serpell (Ed.) The domestic dog (pp. 21–47). Cambridge: Cambridge University Press.

Cordero, D. R., Schneider, R. A., & Helms, J. A. (2002). Morphogenesis of the heart rudiment in Amblystoma. Journal of Experimental Biology, 205, 4457–4468.

Coppinger, L., & Coppinger, R. P. (1982). Scleraxis: A basic helix-loop-helix protein that prefigures skeletal formation during mouse embryogenesis. Development (Cambridge, England), 121, 1099–1110.

David, N. B., Saint-Etienne, L., Tsang, M., Schilling, T. F., & Rosa, F. M. (2002). Requirement for endoderm and FGF3 in ventral head skeleton formation. Development (Cambridge, England), 129, 4457–4468.

Dawson, M., Metzger, K. A., Baier, D. B., & Brainerd, E. L. (2011). Kinematics of the quadrato bone during feeding in mallard ducks. The Journal of Experimental Biology, 214, 2036–2046.

De Beer, G. R. (1930). Embryology and evolution. Oxford: Clarendon Press.

De Beer, G. R. (1937). The development of the vertebrate skull (p. 554). Chicago: University of Chicago Press.

De Beer, G. R. (1947). The differentiation of neural crest cells into visceral cartilages and odontoblasts in amblastoma, and a re-examination of the germ-layer theory. Proceedings of the Royal Society of London. Series B, Biological Sciences, 134, 377–398.

De Beer, G. R. (1954). Embryos and ancestors. Oxford: Clarendon Press.

De Crombrugghe, B., Lefebvre, V., Behringer, R. R., Bl, W., Murakami, S., & Huang, W. (2000). Transcriptional mechanisms of chondrocyte differentiation. Matrix Biol, 19, 389–394.

De Renzi, M. (2009). Developmental and historical patterns at the crossroads in the work of Peter Alberch. In D. Raskin-Gutman, & M. De Renzi (Eds), Peter Alberch: The creative trajectory of an evo-devo biologist (pp. 45–66). Valencia: Universidad de Valencia.

DeLeyhe-Bourgeois, C., Rama, N., Brito, J., Le Douarin, N., & Mehlen, P. (2014). Sonic Hedgehog promotes the survival of neural crest cells by limiting apoptosis induced by the dependence receptor CDON during branchial arch development. Biochemical and Biophysical Research Communications, 452, 655–660.

Depew, M. J., & Compagnucci, C. (2008). Tweaking the hinge and caps: Testing a model of the organization of jaws. Journal of Experimental Zoology. Part B, Molecular and Developmental Evolution, 310, 315–335.

Depew, M. J., Liu, J. K., Long, J. E., Presley, R., Mesenes, J. J., Pedersen, R. A., & Rubenstein, J. L. (1999). Dlx5 regulates regional development of the branchial arches and sensory capsules. Development (Cambridge, England), 126, 3831–3846.

Depew, M. J., Lufkin, T., & Rubenstein, J. L. (2002). Specification of jaw subdivisions by Dlx genes. Science (New York,N.Y.), 298, 381–385.

Depew, M. J., & Simpson, C. A. (2006). 21st century neontology and the comparative development of the vertebrate skull. Developmental Dynamics: An Official Publication of the American Association of Anatomists, 235, 1256–1291.

Derynck, R., Plek, E., Schneider, R. A., Choy, L., & Alliston, T. (2008). TGF-β family signalling in mesenchymal differentiation. In R. Derynck, & K. Miyazono (Eds), The TGF-beta family (pp. 613–666). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press.

Detwiler, S. R. (1930). Observations upon the growth, function, and nerve supply of limbs when grafted to the head of salamander embryos. Journal of Experimental Zoology, 55, 319–379.

Dhouailly, D. (1967). Analysis of the factors in the specific differentiation of the neoptile feathers in the duck and chicken. Journal of Embryology and Experimental Morphology, 18, 389–400.

Dhouailly, D. (1970). The determination of specific differentiation of neoptile and teleoptile feathers in the chick and the duck. Journal of Embryology and Experimental Morphology, 24, 73–94.

Dhouailly, D. (1973). Dermo-epidermal interactions between birds and mammals: Differentiation of cutaneous appendages. Journal of Embryology and Experimental Morphology, 30, 587–603.

Dhouailly, D. (1975). Formation of cutaneous appendages in dermo-epidermal recombinations between reptiles, birds and mammals. Wilhelm Roux’s Archives of Developmental Biology, 177, 223–340.

Dhouailly, D., & Sawyer, R. H. (1984). Avian scale development. XI. Initial appearance of the dermal defect in scaleless skin. Developmental Biology, 105, 343–350.

Donoghue, P. C., Graham, A., & Kelsch, R. N. (2008). The origin and evolution of the neural crest. Bioessays: News and Reviews in Molecular, Cellular and Developmental Biology, 30, 530–541.

Dorris, F. (1938). The production of pigment in vitro by chick neural crest. Wilhelm Roux ‘s Archiv Fur Entwicklungsmechanik Der Organismen, 138, 323–334.

Doulfexi, A. E., & Mina, M. (2008). Signaling pathways regulating the expression of Prx1 and Prx2 in the chick mandibular mesenchyme.
Lan, Y., & Jiang, R. (2009). Sonic hedgehog signaling regulates reciprocal epithelial-mesenchymal interactions controlling palatal outgrowth. Development (Cambridge, England), 136, 1387–1396.

Landacre, F. L. (1921). The fate of the neural crest in the head of theurodeles. The Journal of Comparative Neurology, 33, 1–43.

Lande, R. (1979). Quantitative genetic analysis of multivariate evolution, applied to brain:body size allometry. Evolution, 33, 402–416.

Langille, R. M., & Hall, B. K. (1993). Pattern formation and the neural crest. In J. Hanke, & B. K. Hall (Eds.), The skull (pp. 77–111). Chicago: University of Chicago Press.

Larsen, C. W., Zeltser, L. M., & Lumsden, A. (2001). Boundary formation and compartment in the avian diencephalon. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 21, 4699–4711.

Le Douarin, N. M. (1973). A biological cell labelling technique and its use in experimental embryology. Developmental Biology, 30, 217–222.

Le Douarin, N., & McLaren, A. (1984).

Le Douarin, N., & Teillet, M. M. (1974). Experimental analysis of the Lucas, A. M., & Stettenheim, P. R. (1972).

Lufkin, T., Mark, M., Hart, C., Dollé, P., Lemeur, M., & Chambon, P. (1992). Homeotic transformation of the occipital bones of the skull by ectopic expression of a homeobox gene. Nature, 359, 835–841.

Lumb, R., Buckberry, S., Secker, G., Lawrence, D., & Schwarz, Q. (2017). Transcriptome profiling reveals expression signatures of cranial nerve crest cells arising from different axial levels. BMC Developmental Biology, 17, 5.

Lumer, H. (1940). Evolutionary allometry in the skeleton of the domesticated dog. The American Naturalist, 74, 439–467.

Lumsden, A. G. (1988). Spatial organization of the epithelium and the role of neural crest cells in the initiation of the mammalian tooth germ. Development (Cambridge, England), 103 Suppl, 155–169.

Luo, G., Hofmann, C., Bronckers, A. L., Sohocki, M., Bradley, A., & Karsenty, G. (1995). BMP-7 is an inducer of nephrogenesis, and is also required for eye development and skeletal patterning. Genes & Development, 9, 2808–2820.

Lwigale, P. Y. (2001). Embryonic origin of avian corneal sensory nerves. Developmental Biology, 239, 323–337.

Lwigale, P. Y., Conrad, G. W., & Bronner-Fraser, M. (2004). Graded potential of neural crest to form cornea, sensory neurons and cartilage along the rostrocaudal axis. Development (Cambridge, England), 131, 1979–1991.

Lwigale, P. Y., Cressy, P. A., & Bronner-Fraser, M. (2005). Corneal keratoocytes retain neural crest progenitor cell properties. Developmental Biology, 288, 284–293.

Lwigale, P. Y., & Schneider, R. A. (2008). Other chimeras: Quail-duck and mouse-chick. Methods in Cell Biology, 87, 59–74.

Lynch, N., & Hill, A. (1964). Theoretical foundations of quantitative genetic analysis of multivariate evolution. The American Naturalist, 98, 101–121.

Lynch, W. H., & Owsley, E. E. (1976). An approach to the theoretical foundations of quantitative genetic analysis of multivariate evolution. American Naturalist, 111, 437–456.

Lynch, W. H., & Owsley, E. E. (1977). An approach to the theoretical foundations of quantitative genetic analysis of multivariate evolution. American Naturalist, 112, 785–802.

Lynch, W. H., & Owsley, E. E. (1978). An approach to the theoretical foundations of quantitative genetic analysis of multivariate evolution. American Naturalist, 114, 917–933.

Lynch, W. H., & Owsley, E. E. (1979). An approach to the theoretical foundations of quantitative genetic analysis of multivariate evolution. American Naturalist, 114, 953–966.

Lynch, W. H., & Owsley, E. E. (1980). An approach to the theoretical foundations of quantitative genetic analysis of multivariate evolution. American Naturalist, 117, 597–605.

Lynch, W. H., & Owsley, E. E. (1981). An approach to the theoretical foundations of quantitative genetic analysis of multivariate evolution. American Naturalist, 118, 337–356.

Lynch, W. H., & Owsley, E. E. (1982). An approach to the theoretical foundations of quantitative genetic analysis of multivariate evolution. American Naturalist, 119, 195–215.

Lynch, W. H., & Owsley, E. E. (1983). An approach to the theoretical foundations of quantitative genetic analysis of multivariate evolution. American Naturalist, 122, 23–44.

Lynch, W. H., & Owsley, E. E. (1984). An approach to the theoretical foundations of quantitative genetic analysis of multivariate evolution. American Naturalist, 129, 313–335.

Lynch, W. H., & Owsley, E. E. (1985). An approach to the theoretical foundations of quantitative genetic analysis of multivariate evolution. American Naturalist, 130, 389–408.

Lynch, W. H., & Owsley, E. E. (1986). An approach to the theoretical foundations of quantitative genetic analysis of multivariate evolution. American Naturalist, 131, 332–352.

Lynch, W. H., & Owsley, E. E. (1987). An approach to the theoretical foundations of quantitative genetic analysis of multivariate evolution. American Naturalist, 132, 651–674.

Lynch, W. H., & Owsley, E. E. (1988). An approach to the theoretical foundations of quantitative genetic analysis of multivariate evolution. American Naturalist, 133, 89–107.

Lynch, W. H., & Owsley, E. E. (1989). An approach to the theoretical foundations of quantitative genetic analysis of multivariate evolution. American Naturalist, 134, 229–250.

Lynch, W. H., & Owsley, E. E. (1990). An approach to the theoretical foundations of quantitative genetic analysis of multivariate evolution. American Naturalist, 136, 390–404.

Mangiardi, G. (1976). Malformations of the cranial neural crest. Journal of Experimental Zoology, 195, 229–245.

Mangold, O. (1923). Transplantationsversuche zur Frage der Spezifität und Entwicklungsmechanik in der Bildung der Keimblätter. Wilhelm Roux’ Archiv Für Entwicklungsmechanik Der Organismen, 111, 593–665.

Marcucio, R. S., Young, N. M., Hu, D., & Hallgrimsson, B. (2011). Mechanical design patterns of cranial neural crest cells arising from different axial levels. Development, 138, 3333–3343.

Mangold, O., & Seidel, F. (1927). Homoplastische und heteroplastische Verschmelzung ganzer tritonkeime. Wilhelm Roux’ Archiv Für Entwicklungsmechanik Der Organismen, 111, 593–665.

Marcucio, R. S., Cordero, D. R., Hu, D., & Helms, J. A. (2005). Mechanical interactions coordinating the development of the forebrain and face. Developmental Biology, 284, 48–61.

Marcus, L. F. (1996). Advances in morphometrics. New York, NY: Plenum Press.

Massague, J., & Wotton, D. (2000). Transcriptional control by the TGF-beta/Smad signaling system. The Embo Journal, 19, 1745–1754.

Mathew, S. J., Hansen, J. M., Merrell, A. J., Murphy, M. M., Lawson, J. A., Hutcheson, D. A., ... Kardon, G. (2011). Connective tissue fibroblasts and Tcf4 regulate myogenesis. Development (Cambridge, England), 138, 371–384.

Matsuoka, T., Aihberg, P. E., Kessaris, N., Iannarelli, P., Dennehy, U., Richardson, W. D., ... Koentges, G. (2005). Neural crest origins of the neck and shoulder. Nature, 436, 347–355.

Mayerson, P. L., & Fallon, J. F. (1981). The spatial pattern and temporal sequence in which feather germs arise in the white Leghorn chick embryo. Developmental Biology, 89, 259–267.

McGurk, P. A.-O., Swartz, M. A.-O., Chen, J. W., Galloway, J. L., & Eberhart, J. K. (2017). In vivo zebrafish morphogenesis shows Cyp26b1
Sohal, G. S., Knox, T. S., Allen, J. C., Jr., Arumugam, T., Campbell, L. R., & Yamashita, T. (1985). Development of the trophic nucleus in quail and comparative study of the trophic nucleus, nerve, and innervation of the superior oblique muscle in quail, chick, and duck. The Journal of Comparative Neurology, 239, 227–236.

Solem, R. C., Eames, B. F., Tokita, M., & Schneider, R. A. (2011). Mesenchymal and mechanical mechanisms of secondary cartilage induction. Developmental Biology, 356, 28–39.

Solloway, M. J., Dudley, A. T., Bikoff, E. K., Lyons, K. M., Hogan, B. L., & Robertson, E. J. (1998). Mice lacking Bmp6 function. Developmental Genetics, 22, 321–339.

Song, H. K., Lee, S. H., & Goetinck, P. F. (2004). FGF-2 signaling is sufficient to induce dermal condensations during feather development. Developmental Dynamics: An Official Publication of the American Association of Anatomists, 231, 741–749.

Song, H. K., & Sawyer, R. H. (1996). Dorsal dermis of the scaleless (sc/sc) embryo directs normal feather pattern formation until day 8 of development. Developmental Dynamics: An Official Publication of the American Association of Anatomists, 205, 82–91.

Song, H., Wang, Y., & Goetinck, P. F. (1996). Fibroblast growth factor 2 can replace ectodermal signaling for feather development. Proceedings of the National Academy of Sciences of the United States of America, 93, 10246–10249.

Song, Y., Hui, J. N., Fu, K. K., & Richman, J. M. (2004). Control of retinoic acid synthesis and FGF expression in the nasal pit is required for pattern the craniofacial skeletal. Developmental Biology, 276, 313–329.

Sonu, V. C. (1979). The role of kinesis and mechanical advantage in the feeding apparatus of some partridges and quails. Annales of Zoology, 15, 103–110.

Spemann, H. (1918). Über die determination der ersten organanlagen des amphibiembryos 1–VI. Archiv Für Entwicklungsmechanik Der Organismen, 43, 448–555.

Spemann, H. (1921). Die erzeugung tierischer chimären durch heteroplasmische embryonale transplantation zwischen triton cristatus und taeniathera. Archiv Für Entwicklungsmechanik Der Organismen, 48, 533–570.

Spemann, H. (1924). Entwicklung and induction. New Haven: Yale University Press.

Spemann, H., & Mangold, H. (1924). Induction of embryonic primordia by implantation of organizers from a different species (pp. 144–184). New York, NY: Hafner.

Spemann, H., & Schotte, O. (1932). Über xenoplastische Transplantation als Mittel zur Analyse der embryovalen Induktion. Die Naturwissenschaften, 20, 463–467.

Square, T., Jandzik, D., Romasek, M., Cerny, R., & Medeiros, D. M. (2017). Involvement of Hedgehog and FGF signalling in the lamprey telencephalon: Evolution of regionalization and dorsoventral patterning of the vertebrate forebrain. Development (Cambridge, England), 138, 1217–1226.

Sugih, H., Grimaldi, A., Li, J., Parada, C., Vu-Ho, T., Feng, J., ... Chai, Y. (2017). The Dlx5–FGF10 signaling cascade controls cranial neural crest and myoblast interaction during oropharyngeal patterning and development. Development (Cambridge, England), 144, 4037–4045.

Swett, F. H. (1930). The permanence of limb-axis polarity. Journal of Experimental Zoology, 55, 87–99.

Szabo-Rogers, H. L., Geetha-Loganathan, P., Nimmagadda, S., Fu, K. K., & Richman, J. M. (2008). FGF signals from the nasal pit are necessary for normal facial morphogenesis. Developmental Biology, 318, 289–302.

Tak, H. J., Park, T. J., Piao, Z., & Lee, S. H. (2017). Separate development of the maxilla and mandible is controlled by regional signaling of the maxillomandibular junction during avian development. Developmental Dynamics: An Official Publication of the American Association of Anatomists, 246, 28–40.

Takio, Y., Pasqualetti, M., Kuraku, S., Hirano, S., Rijli, F. M., & Kuratani, S. (2004). Evolutionary biology: Lamprey Hox genes and the evolution of jaws. Nature, 429, 1.

Tanda, N., Ohuchi, H., Yoshioka, H., Noji, S., & Nohno, T. (1995). A chicken Wnt gene, Wnt-11, is involved in dermal development. Biochemical and Biophysical Research Communications, 211, 123–129.

Tang, S. Y., Herber, R. P., Ho, S. P., & Alliston, T. (2012). Matrix metalloproteinase-13 is required for osteocytic perilacunar remodeling and maintains bone fracture resistance. Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research, 27, 1936–1950.

Tao, H., Yoshimoto, Y., Yoshioka, H., Nohno, T., Noji, S., & Ohuchi, H. (2002). FGF10 is a mesenchymally derived stimulator for epidermal development in the chick embryonic skin. Mechanisms of Development, 116, 39–49.

Tavares, A. L. P., Cox, T. C., Maxson, R. M., Ford, H. L., & Clouthier, D. E. (2012). Ectodermal-derived Endothelin1 is required for proper maxillary development. Development (Cambridge, England), 139, 1091–1101.

Teitelbaum, S. L. (2000). Bone resorption by osteoclasts. Science (New York, N.Y.), 289, 1504–1508.

Teitelbaum, S. L., Tondravi, M. M., & Ross, F. P. (1997). Osteoclasts, macrophages, and the molecular mechanisms of bone resorption. Journal of Leukocyte Biology, 61, 381–388.

Thesleff, I., & Sharpe, P. (1997). Signalling networks regulating dental development. Mechanisms of Development, 67, 111–123.

Thomas, D. M., Johnson, S. A., Sims, N. A., Trivett, M. K., Slavin, J. L., Rubin, B. P., ... Hinds, P. W. (2004). Terminal osteoblast differentiation, mediated by runx2 and p27kip1, is disrupted in osteosarcoma. The Journal of Cell Biology, 167, 925–934.

Thompson, D. W. (1917). On growth and form. Cambridge: University Press.

Thompson, D. W. (1952). On growth and form. Cambridge: University Press (1116 pages).

Stone, L. S. (1930). Heteroplastic transplantation of eyes between the larvae of two species of Amblystoma. Journal of Experimental Zoology, 55, 193–216.

Stone, L. S. (1932). Transplantation of hyobranchial mesodermot, including the right lateral anlage of the second basibranchium, in Amblystoma punctatum. Journal of Experimental Zoology, 62, 109–123.

Stone, L. S., & Dineen, F. L. (1940). Experimental studies on the relation of the optic vesicle and cup to lens formation in Amblystoma punctatum. Journal of Experimental Zoology, 83, 95–125.

Subramanian, A., & Schilling, T. F. (2015). Tendon development and musculoskeletal assembly: Emerging roles for the extracellular matrix. Development (Cambridge, England), 142, 4191–4204.

Sugahara, F., Aota, S., Kuraku, S., Murakami, Y., Takio-Ogawa, Y., Hirano, S., & Kuratani, S. (2011). Involvement of Hedgehog and FGF signalling in the lamprey telencephalon: Evolution of regionalization and dorsoventral patterning of the vertebrate forebrain. Development (Cambridge, England), 138, 1217–1226.

Song, Y., Hui, J. N., Fu, K. K., & Richman, J. M. (2004). Evolutionary biology: Lamprey Hox genes and the evolution of jaws. Nature, 429, 1.

Tao, H., Yoshimoto, Y., Yoshioka, H., Nohno, T., Noji, S., & Ohuchi, H. (2002). FGF10 is a mesenchymally derived stimulator for epidermal development in the chick embryonic skin. Mechanisms of Development, 116, 39–49.

Tavares, A. L. P., Cox, T. C., Maxson, R. M., Ford, H. L., & Clouthier, D. E. (2017). Negative regulation of endothelin signaling by SIX1 is required for proper maxillary development. Development (Cambridge, England), 144, 2021–2031.

Tavares, A. L., Garcia, E. L., Kuhn, K., Woods, C. M., Williams, T., & Clouthier, D. E. (2012). Ectodermal-derived Endothelin1 is required for patterning the distal and intermediate domains of the mouse mandibular arch. Developmental Biology, 371, 47–56.

Teitelbaum, S. L. (2000). Bone resorption by osteoclasts. Science (New York, N.Y.), 289, 1504–1508.

Teitelbaum, S. L., Tondravi, M. M., & Ross, F. P. (1997). Osteoclasts, macrophages, and the molecular mechanisms of bone resorption. Journal of Leukocyte Biology, 61, 381–388.

Thesleff, I., & Sharpe, P. (1997). Signalling networks regulating dental development. Mechanisms of Development, 67, 111–123.
Trainor, P., & Krumlauf, R. (2000). Plasticity in mouse neural crest cells.

Tosney, K. W. (1982). The segregation and early migration of cranial neural crest cells.

Tonegawa, Y. (1973). Inductive tissue interactions in beak of a chick-embryo.

Twitty, V. C. (1934). Growth correlations in amphibia studied by the method of transplantation. Cold Spring Harbor Symposia on Quantitative Biology, 2, 145–156.

Twitty, V. C. (1936). Correlated genetic and embryological experiments on Triturus. I and II. Journal of Experimental Zoology, 74, 239–302.

Twitty, V. C. (1945). The developmental analysis of specific pigment patterns. Journal of Experimental Zoology, 100, 141–178.

Twitty, V. C. (1966). Of Scientists and Salamanders. San Francisco: W. H. Freeman and Company.

Twitty, V. C., & Bodenstein, D. (1939). Correlated genetic and embryological experiments on Triturus. III. Further transplantation experiments on pigment development. IV. The study of pigment cell behavior in vitro. Journal of Experimental Zoology, 81, 357–398.

Twitty, V. C., & Schwind, J. L. (1931). The growth of eyes and limbs transplanted heteroplastically between two species of Amblystoma. Journal of Experimental Zoology, 59, 61–86.

Tyler, M. S. (1978). Epithelial influences on membrane bone formation in the maxilla of the embryonic chick. The Anatomical Record, 192, 225–233.

Tyler, M. S. (1983). Development of the frontal bone and cranial meninges in the embryonic chick: An experimental study of tissue interactions. The Anatomical Record, 206, 61–70.

Tzahor, E., Kempf, H., Mootooosamy, R. C., Poon, A. C., Abzhanov, A., Tabin, C. J., ... Lasar, A. B. (2003). Antagonists of Wnt and BMP signaling promote the formation of vertebrate head muscle. Genes & Development, 17, 3087–3099.

Urist, M. R. (1965). Bone: Formation by autoinduction. Science (New York, N.Y.), 150, 893–899.

Uygur, A., Young, J., Huycke, T. R., Koska, M., Briscoe, J., & Tabin, C. J. (2016). Scaling pattern to variations in size during development of the vertebrate neural tube. Developmental Cell, 37, 127–135.

Van den Heuvel, W. F. (1992). Kinetics of the skull in the chicken (Gallus Gallus Domesticus). Netherlands Journal of Zoology, 42, 561–582.

Veitch, E., Begbie, J., Schilling, T. F., Smith, M. M., & Graham, A. (1999). Pharyngeal arch patterning in the absence of neural crest. Current Biology, 9, 1481–1484.

Viallet, J. P., Prin, F., Olivera-Martinez, I., Hirsinger, E., Pourquié, O., & Dhоuailli, D. (1998). Chick Delta-1 gene expression and the formation of the feather primordia. Mechanisms of Development, 72, 159–168.

Von Bonin, G. (1937). Brain-weight and body-weight of mammals. Journal of General Psychology, 16, 379–389.

Wachtler, F., & Jacob, M. (1986). Origin and development of the cranial skeletal muscles. Bibliotheca Anatomica, 29, 24–46.

Wada, N., Javidan, Y., Nelson, S., Carney, T. J., Kelsh, R. N., & Harada, T. (2013). Molecular and cellular changes associated with the evolution of novel jaw muscles in parrots. Proceedings of Biological Sciences, 280, 20122319.

Tokita, M., & Schneider, R. A. (2009). Developmental origins of species-specific muscle pattern. Developmental Biology, 331, 311–325.

Tonegawa, Y. (1973). Inductive tissue interactions in beak of a chick-embryo. Development, Growth and Differentiation, 15, 57–71.

Tosney, K. W. (1982). The segregation and early migration of cranial neural crest cells in the avian embryo. Developmental Biology, 89, 13–24.

Trainor, P., & Krumlauf, R. (2000). Plasticity in mouse neural crest cells reveals a new patterning role for cranial mesoderm. Nature Cell Biology, 2, 96–102.

Trainor, P. A., Ariza-McNaughton, L., & Krumlauf, R. (2002). Role of the isthmus and FGFs in resolving the paradox of neural crest plasticity and prepatternig. Science (New York, N.Y.), 295, 1288–1291.

Trainor, P. A., & Krumlauf, R. (2001). Hox genes, neural crest cells and branchial arch patterning. Current Opinion in Cell Biology, 13, 698–705.

Trainor, P. A., Melton, K. R., & Manzanares, M. (2003). Origins and plasticity of neural crest cells and their roles in jaw and craniofacial evolution. The International Journal of Developmental Biology, 47, 541–553.

Trainor PA, Sobieszczuk D, Wilkinson D, Krumlauf R. (2002b). Signalling pathways. Development, Growth & Differentiation, 44, 157–170.

Trainor, P. A., & Lumsden, A. (2004). Neural crest cells provide...
Wang, Y. H., Upholt, W. B., Sharpe, P. T., Kollar, E. J., & Mina, M. (1998). Odontogenic epithelium induces similar molecular responses in chick and mouse mandibular mesenchyme. Developmental Dynamics: An Official Publication of the American Association of Anatomists, 213, 386–397.

Webb, J. F., & Noden, D. M. (1993). Ectodermal placodes: Contributions to the development of the vertebrate head. American Zoologist, 33, 434–447.

Wedden, S. E. (1987). Epithelial-mesenchymal interactions in the development of chick facial primordia and the target of retinoid action. Development (Cambridge, England), 99, 341–351.

Wessells, N. K. (1965). Morphology and proliferation during early feather development. Developmental Biology, 12, 131–153.

West-Eberhard, M. J. (1989). Phenotypic plasticity and the origins of diversity. Annual Review of Ecology and Systematics, 20, 249–278.

West-Eberhard, M. J. (2003). Developmental plasticity and evolution. Oxford: New York: Oxford University Press.

Wedelitz, R. B., & Chuang, C. M. (1999). Early events in skin appendage formation: Induction of epithelial placodes and condensation of dermal mesenchyme. The Journal of Investigative Dermatology. Symposium Proceedings, 4, 302–306.

Wedelitz, R. B., Jiang, T. X., Chen, C. W., Stott, N. S., & Chuang, C. M. (1999). Wnt-7a in feather morphogenesis: Involvement of anterior-posterior asymmetry and proximal-distal elongation demonstrated with an in vitro reconstitution model. Development, 126, 2577–2587.

Wedelitz, R. B., Jiang, T. X., Lu, J., & Chuang, C. M. (2000). beta-catenin in epithelial morphogenesis: Conversion of part of avian foot scales into feather buds with a mutated beta-catenin. Developmental Biology, 219, 98–114.

Wedelitz, R. B., Jiang, T. X., Noveen, A., Chen, C. W., & Chuang, C. M. (1996). FGF induces new feather buds from developing avian skin. The Journal of Investigative Dermatology, 107, 797–803.

Wedelitz, R. B., Jiang, T. X., Noveen, A., Ting-Bereth, S. A., Yin, E., Jung, H. S., & Chuang, C. M. (1997). Molecular histology in skin appendage morphogenesis. Microscopy Research and Technique, 38, 452–465.

Wilkins, A. S., Wrangham, R. W., & Fitch, W. T. (2014). The "domestication syndrome" in mammals: A unified explanation based on neural crest cell behavior and genetics. Genetics, 197, 795–808.

Williams, R. M., Senanayake, U., Artibani, M., Taylor, G., Wells, D., Ahmed, A. A., & Sauka-Spengler, T. (2018). Genome and epigenome engineering CRISPR toolkit for in vivo modulation of cis-regulatory interactions and gene expression in the chicken embryo. Development, 145, dev160333.

Wilson, J., & Tucker, A. S. (2004). Fgf and Bmp signals repress the expression of Bapx1 in the mandibular mesenchyme and control the position of the developing jaw joint. Developmental Biology, 266, 138–150.

Withington, S., Beddington, R., & Cooke, J. (2001). Foregut endoderm is required at head process stages for anteriormost neural patterning in chick. Development (Cambridge, England), 128, 309–320.

Woronowicz, K. C., Gline, S. E., Herfat, S. T., Fields, A. J., & Schneider, R. A. (2018). FGF and TGFβ signaling link form and function during jaw development and evolution. Developmental Biology, https://doi.org/10.1016/j.ydbio.2018.05.002.

Wozney, M. J., Rosen, V., Celeste, A. J., Mitsock, L. M., Whitters, M. J., Kriz, R. W., … Wang, E. A. (1988). Novel regulators of bone formation: Molecular clones and activities. Science (New York, N.Y.), 242, 1528–1534.

Wu, P., Jiang, T. X., Shen, J. Y., Wedelitz, R. B., & Chuang, C. M. (2006). Morphoregulation of avian beaks: Comparative mapping of growth zone activities and morphological evolution. Developmental Dynamics: An Official Publication of the American Association of Anatomists, 235, 1400–1412.

Wu, P., Jiang, T. X., Suksaweeang, S., Wedelitz, R. B., & Chuang, C. M. (2004). Molecular shaping of the beak. Science (New York, N.Y.), 305, 1465–1466.

Xia, S. L., & Ferrier, J. (1996). Localized calcium signaling in multinucleated osteoclasts. Journal of Cellular Physiology, 167, 148–155.

Xiong, J., & O’Brien, C. A. (2012). Osteocyte RANKL: New insights into the control of bone remodeling. Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research, 27, 499–505.

Xiong, J., Piemontese, M., Thostenson, J. D., Weinstein, R. S., Manolagas, S. C., & O’Brien, C. A. (2014). Osteocyte-derived RANKL is a critical mediator of the increased bone resorption caused by dietary calcium deficiency. Bone, 66, 146–154.

Xu, Q., Jamnicky, H., Hu, D., Green, R. M., Marcucio, R. S., Hallgrimsson, B., & Mio, W. (2015). Correlations between the morphology of sonic hedgehog expression domains and embryonic craniofacial shape. Evolutionary Biology, 42, 379–386.

Yamashita, T., & Sohal, G. S. (1986). Development of smooth and skeletal muscle cells in the iris of the domestic duck, chick and quail. Cell and Tissue Research, 244, 121–131.

Yamashita, T., & Sohal, G. S. (1987). Embryonic origin of skeletal muscle cells in the iris of the duck and quail. Cell and Tissue Research, 249, 31–37.

Yang, L., O’Neill, P., Martin, K., Maass, J. C., Vassilev, V., Ladher, R., & Groves, A. K. (2013). Analysis of FGF-dependent and FGF-independent pathways in otic placode induction. PLoS One, 8, e55011.

Yao, T., Ohtani, K., Kuratani, S., & Wada, H. (2011). Development of lamprey mucocartilage and its dorsal-ventral patterning by endothelin signaling, with insight into vertebrate jaw evolution. Journal of Experimental Zoology. Part B, Molecular and Developmental Evolution, 316, 339–346.

Yasui, K., & Hayashi, Y. (1967). Morphogenesis of the beak of the chick embryo: Histological, histochemical and autoradiographic studies. Embryologia, 10, 42–74.

Yoshizawa, M., Hixon, E., & Jeffery, W. R. (2018). Neural crest transplantation reveals key roles in the evolution of cavefish development. Integrative and Comparative Biology, 52, icy006.

Young, N. M., Chong, H. J., Hu, D., Hallgrimsson, B., & Marcucio, R. S. (2010). Quantitative analyses link modulation of sonic hedgehog signaling to continuous variation in facial growth and shape. Development (Cambridge, England), 137, 3405–3409.

Young, D. W., Hassan, M. Q., Pratap, J., Galindo, M., Zaidi, S. K., Lee, S. H., … Stein, G. S. (2007). Mitotic occupancy and lineage-specific transcriptional control of mRNA genes by Runx2. Nature, 445, 442–446.

Young, N. M., Hu, D., Lainoff, A. J., Smith, F. J., Diaz, R., Tucker, A. S., … Marcucio, R. S. (2014). Embryonic bauplans and the developmental origins of facial diversity and constraint. Development (Cambridge, England), 141, 1059–1063.

Yu, M., Wu, P., Wedelitz, R. B., & Chuang, C. M. (2002). The morphogenesis of feathers. Nature, 420, 308–312.

Yu, M., Yue, Z., Wu, P., Wu, D. Y., Mayer, J. A., Medina, M., … Chuang, C. M. (2004). The developmental biology of feather follicles. The International Journal of Developmental Biology, 48, 181–191.

Zacchei, A. M. (1961). The embryonic development of the Japanese quail (Coturnix coturnix japonica). Archivio Italiano Di Anatomia e Di Embriologia. Italian Journal of Anatomy and Embryology, 66, 36–62.

Zavitz, K. H., & Zipursky, S. L. (1997). Controlling cell proliferation in differentiating tissues: Genetic analysis of negative regulators of G1→S-phase progression. Current Opinion in Cell Biology, 9, 773–781.

Zayzafoun, M. (2006). Calcium/calcmodulin signaling controls osteoblast growth and differentiation. Journal of Cellular Biochemistry, 97, 56–70.

Zelditch, M. (2004). Geometric morphometrics for biologists: A primer. Amsterdam: Boston: Elsevier Academic Press.

Zhang, W., Bergamaschi, D., Jin, B., & Lu, X. (2005). Posttranslational modifications of p27kip1 determine its binding specificity to different cyclins and cyclin-dependent kinases in vivo. Blood, 105, 3691–3698.

Zhao, Q., Eberspaecher, H., Lefebvre, V., & De Crombrugghe, B. (1997). Parallel expression of Sox9 and Col2a1 in cells undergoing chondrogenesis. Developmental Dynamics: An Official Publication of the American Association of Anatomists, 209, 377–386.

Zusi, R. L. (1993). Patterns of diversity in the avian skull. In J. Hanken, & B. K. Hall (Eds.), The skull (pp. 391–437). Chicago: University of Chicago Press.
Zweers, G. (1974). Structure, movement, and myography of the feeding apparatus of the mallard (Anas platyrhynchos L.). A study in functional anatomy. *Netherlands Journal of Zoology*, 24, 323–467.

Zweers, G. A., Gerritsen, A. F. C., & Kranenburg-Voogd, P. J. (1977). Mechanics of feeding of the mallard (Anas platyrhynchos L.; Aves, Anseriformes): The lingual apparatus and the suction-pressure pump mechanism of straining. Basel; New York: S. Karger.

Zweers, G. A., Kunz, G., & Mos, J. (1977). Functional anatomy of the feeding apparatus of the mallard (Anas platyrhynchos L.) structure, movement, electro-myography and electro-neurography. *Annals of Anatomy*, 142, 10–20.

Zwilling, E. (1959). Interaction between ectoderm and mesoderm in duck-chicken limb bud chimaeras. *The Journal of Experimental Zoology*, 142, 521–532.

How to cite this article: Schneider RA. Neural crest and the origin of species-specific pattern. genesis. 2018;56:e23219. https://doi.org/10.1002/dvg.23219