of the tissue associated with the brain and paired sense organs develops from tissue that was not present in cephalochordates. The origin of neural crest and placode tissue thus become key to the origin of craniates (N. D. Holland et al. 1996).

Many of the primitive attributes of cephalochordates may be correlated with the absence of particular developmental genes. For example, neural crest cells are associated with the vertebrate *Hox* genes *Hoxa-1* and *Hoxa-3,* which are not present in *Branchiostoma,* although their paralogues, *Hoxb-1* and *Hoxb-3,* are (Holland 1992; Holland et al. 1994). The origin of neural crest may thus be linked with the duplication of gene clusters that produced these new *Hox* genes at the base of the vertebrate lineage (Peterson 1994). Several other genes also appear to have undergone duplication during the transition between cephalochordates and craniates. These include some homeobox genes that are not part of the *Hox* clusters (termed *non-Hox* or *diverged homeobox* genes by Ruddle et al. 1994a). Among these are members of the *Msx* gene family. Three are known in mammals: Two are expressed in neural crest–derived mesenchymal tissue involved with branchial arch development, palate formation, tooth morphogenesis, and development of the paired eyes; only a single gene is recognized in *Branchiostoma.* Others are members of the family of engrailed genes, within which the vertebrate gene *En-2,* not present in cephalochordates, has an important role in hindbrain formation (Holland 1992), and its expression extends as far forward as the midbrain (Langille and Hall 1993).

Although not limited to the head region, another major change between cephalochordates and craniates that can be associated with gene duplication is expressed in the development and adult structure of striated muscles. Among vertebrates, the development of striated muscles involves fusion of the precursors of muscle cells, the myoblasts, into much larger cells containing many nuclei. Cephalochordates, in contrast, have simple, mononucleate muscle cells resembling the embryonic myoblasts of vertebrates. The different patterns of development may be attributed to the duplication of genes within the family that controls formation of alkali myosin light chain molecules in vertebrate muscles. Holland et al. (1995) found only a single member of this gene family in *Branchiostoma.*

The duplication of *Hox* cluster genes and other genes controlling major developmental processes certainly played a key role in the origin of craniates. There was apparently another episode of gene duplication between primitive jawless fish and the modern groups of jawed vertebrates, although the magnitude and timing of the latter process cannot be established without additional knowledge of living agnathans and the sharks and their relatives. In contrast, there is no evidence for the appearance of new *Hox* genes among the vast assemblage of bony fish and terrestrial vertebrates during the past 400 million years, despite such radical morphological changes as the emergence of paired limbs and their continuing adaptation to a host of different environments. Sean Carroll (1995) argues that all the structural diversity within these groups may be attributed to alterations, not in the *Hox* genes themselves, but through modifications of regulatory genes that alter the timing, place, and manner of expression of the *Hox* genes. These fall into two large categories: changes in the regulation of *Hox* genes themselves, and changes in the interactions between *Hox* gene products and the genes they regulate. It is probably this latter process that led to most of the transformations that we can observe in the fossil record of vertebrates.