In all animals – nematodes, flies, frogs, mice, chickens and other species investigated to a lesser extent – Hox genes appear to control the organization of the embryo along the anterior–posterior axis. The structure that forms in a particular part of the body (legs, wings, antennae, ribs and so on) is strongly influenced by which Hox protein is produced there. Homeotic mutants can have missing body parts or, more spectacularly, one part of the body transformed into a copy of another.

Hox genes have in common a similar homeo-domain (HD), a well-conserved DNA-binding motif. Hox genes are expressed in the same order along the body axis as their physical position on the chromosome. The sequence similarities with corresponding genes in other animals, together with the cluster organization, allow classification into anterior, central and posterior gene types. Variations include Amphioxus with at least ten genes, nematodes with a single cluster of four genes, flies with one split cluster of eight genes, and vertebrates with clusters containing 39 genes. The clustered Hox genes encode HDs that are closely related compared with most other HDs. The clusters are thought to have arisen by divergence from a smaller number of ancestral genes. The exact evolutionary relationship between HOX proteins, as determined by cladistic methods, are still in flux as new data are obtained.

The ability of a protein to carry, encoded within its structure, the recipe for a body structure is still mysterious and fascinating. HOX proteins are transcription factors, but how a ‘head’ HOX protein regulates transcription differently from a ‘thorax’ HOX protein continues to be a key question, particularly because anterior proteins remain anterior proteins, even across vast evolutionary distances. The basis of specificity is thought to be, in part, distinct DNA-binding properties and, in part, contacts with other proteins. The best-studied example of a Hox protein cofactor is the Drosophila extradenticle (EXD) protein, called PBX in vertebrates where it was discovered for its role in human leukemia (reviewed in Ref. 17). In flies and in mice, EXD/PBX binds cooperatively with the LADIAL/HOX1 proteins to DNA sequences used for positive autoregulation. EXD also works together with UBX protein to control a downstream target in the fly mesoderm.

Hox genes in evolution: protein surfaces and paralog groups

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The clustered Hox genes, which encode homeo-domain transcription factors, control cell fates along the anterior–posterior axis. Differences between Hox proteins cause differences between body parts. Vertebrates have 13 Hox subgroups, called paralog groups, which can be correlated with some of the insect and Amphioxus genes, and have remained distinctive for hundreds of millions of years. We identify characteristic residues that define the different paralog groups. Some paralog groups can be recognized by the homeo-domain sequence alone; others only by using characteristic residues outside the homeo-domain. Mapping characteristic residues onto the known homeo-domain crystal structure reveals that most of the homeo-domain amino acids that distinguish paralog groups are oriented away from the DNA, in positions where they might engage in protein–protein interactions.

Hox paralog groups

Mice and humans have four copies of the Hox gene cluster, called Hoxa–d (HOXA–D), which are believed to have arisen during two or three ancient duplication events. Each cluster is located on a different chromosome and each contains a subset of 13 gene types. The types are defined by sequence similarity and are called

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progressively fewer in the anterior. For this reason, loss of HOX function most commonly leads to transformations of posterior structures into anterior ones. Sequence similarities, as well as similarities in expression domains, suggest that paralogous Hox genes sometimes share similar functions. This is best exemplified by the phenotype associated with the mutations of Hoxa3 and Hoxd3 (Refs 19–21). Disruption of the Hoxa3 gene leads to defects in the vertebral arch-derived hyoid bone, thyroid cartilage, thymus and epiglottis. Mutations in Hoxd3 lead to the homeotic transformation of the first cervical vertebra into the adjacent anterior structure. The abnormalities observed in each mutant are distinct. However, in double mutants Hoxa3 and Hoxd3 defects are also exacerbated; the entire first cervical vertebra and the thymus are deleted and the epiglottis phenotype is more severe.

Thus, paralogous genes are believed to be functionally equivalent at least in some contexts. In contrast, genes from different paralog groups have distinct effects on development. This raises the question: which protein structures are common among paralog group members? Although many alignments of HOX proteins have been published, the residues that define paralog groups have not previously been well defined. We have compared more than 150 HOX proteins from a variety of animals to determine which parts of the proteins are specified in each paralog group. We systematically define a ‘characteristic residue’ as an amino acid conserved by all members of one paralog group, but not conserved at that position by any other. The 60 amino acids of the HD were used to align the sequences and, depending on the length of sequence available, comparisons were extended to as many as 100 amino acids on each side of the HD. We find that characteristic residues are sufficient to identify and to distinguish paralog groups uniquely, with some groups having more distinctive features than others. The positions of characteristic residues, inside or around the HD, might constitute contact surfaces for cofactor proteins. Finally, as a test of the usefulness of characteristic residues in classifying HOX proteins, we examine the classification of the distantly related nematode and sea urchin HOX proteins. To what extent the characteristic residues turn out to be conserved among other animals will be seen; some important evolutionary events are likely to be
Box 1. Sources of HOX sequences


HOX1^1* HOX1 Amphiobius (PIR S47600), HOX1 human (E. Boncinelli, pers. commun., HOX1 mouse (SWISS-PROT P00022, HOX1 axolotl (SWISS-PROT P31245), HOX1 chick (SWISS-PROT P31259), HOX1 human (SWISS-PROT P14653), HOX1 mouse (SWISS-PROT P17919), HOX1 dog (PIR S6931), HOX1 mouse (SWISS-PROT Q03822), HOX1 Xenopus (PIR C40656), labeal Drosophila (SWISS-PROT P1105).

HOX2* Amphiobius (PIR S47601), HOX2 chick (SWISS-PROT P06727), HOX2 mouse (SWISS-PROT P31245), HOX2 rat (SWISS-PROT P31246), HOX2 human (SWISS-PROT P14652, P17489, P10913), HOX2 mouse (D. Duboule, pers. commun., HOX2 salмон (SWISS-PROT P0638), proboscipedia Drosophila (SWISS-PROT P11246).

HOX3 Amphiobius (PIR S24762), HOX3 mouse (SWISS-PROT P02831), HOX3 chick (SWISS-PROT P28582), HOX3 human (SWISS-PROT P14651, P17484), HOX3 mouse (SWISS-PROT P09026, P10285), HOX3 Xenopus (SWISS-PROT P31267), HOX3 human (SWISS-PROT P31249), HOX3 mouse (SWISS-PROT P09027), HOX3 dog (SWISS-PROT P18867), HOX3 newt (PIR J1162).

HOX4 Amphiobius (PIR S47602), deformed Drosophila (SWISS-PROT P07548), HOX4 chick (SWISS-PROT P17277), HOX4 human (SWISS-PROT Q00956), HOX4 mouse (SWISS-PROT P06798), HOX4 rat (SWISS-PROT P09635), HOX4 chick (SWISS-PROT P14840), HOX4 human (SWISS-PROT P17483), HOX4 mouse (SWISS-PROT P10084), HOX4 Xenopus (SWISS-PROT P09070), HOX4 mouse (SWISS-PROT P09017), HOX4 mouse (SWISS-PROT Q08624), HOX4 rat (SWISS-PROT P18865), HOX4 zebrafish (SWISS-PROT P22574), HOX4 chick (SWISS-PROT P17276), HOX4 dog (SWISS-PROT P09010), HOX4 mouse (SWISS-PROT P1008).

HOX5 Amphiobius (PIR S47603), HOX5 human (SWISS-PROT P20719), HOX5 mouse (SWISS-PROT P09021), HOX5 salmon (SWISS-PROT P09037), HOX5 zebrafish (SWISS-PROT P90014), HOX5 chick (SWISS-PROT P14839), HOX5 human (SWISS-PROT P09067, P09069), HOX5 mouse (SWISS-PROT P09075), HOX5. Xenopus (SWISS-PROT P90019), HOX5 chick (SWISS-PROT P90074), HOX5 human (SWISS-PROT P90044), HOX5 mouse (SWISS-PROT P30435), HOX5 newt (SWISS-PROT P10020), HOX5 newt (SWISS-PROT P10020).

HOX6 Amphiobius (PIR S50607), HOX6 human (SWISS-PROT P31267), HOX6 mouse (SWISS-PROT P09095), HOX6 zebrafish (SWISS-PROT P31561), HOX6 chick (SWISS-PROT P17509, P09068), HOX6 mouse (SWISS-PROT P09025), HOX6 newt (SWISS-PROT P31562), HOX6 human (SWISS-PROT P09060), HOX6 mouse (SWISS-PROT P10062), HOX6 newt (PIR A14586, P14857), HOX6 Xenopus (SWISS-PROT P32082), HOX6 chick (PIR S08363).

HOX7* HOX7 Amphiobius (PIR S47605), HOX7 human (SWISS-PROT P20661), HOX7 mouse (SWISS-PROT P31268), HOX7 mouse (SWISS-PROT P02830), HOX7 rat (SWISS-PROT P09043), HOX7 Xenopus (SWISS-PROT P09071), HOX7 human (SWISS-PROT P09062), HOX7 mouse (SWISS-PROT P09024), HOX7 rat (SWISS-PROT P09024), HOX7 dog (SWISS-PROT P04476, P09018).

HOX8* HOX8 Amphiobius (PIR S47606), HOX8 chick (SWISS-PROT P25681), HOX8 human (SWISS-PROT P17481), HOX8 mouse (SWISS-PROT P09852), HOX8 rat (SWISS-PROT P18863), HOX8 pig (SWISS-PROT P09708), HOX8 dog (SWISS-PROT P31275), HOX8 chick (SWISS-PROT P09865), HOX8 mouse (SWISS-PROT P31275), HOX8 dog (SWISS-PROT P31275), HOX8 zebrafish (SWISS-PROT P25459), HOX8 dog (SWISS-PROT P25463), HOX8 dog (PIR S09957, S3697).

HOX9 Abdominal B Drosophila (SWISS-PROT P09087), HOX9 Amphiobius (PIR S47607), HOX9 human (SWISS-PROT P31259), HOX9 mouse (SWISS-PROT P09031), HOX9 dog (SWISS-PROT P17482), HOX9 mouse (PIR A52991, HOX9 Xenopus (SWISS-PROT P31272), HOX9 human (SWISS-PROT P24340), HOX9 mouse (SWISS-PROT P28356), HOX9 axolotl (SWISS-PROT P28357).

HOX10 HOX10 human (13), HOX10 human (PIR P31260), HOX10 mouse (SWISS-PROT P31310), HOX10 human (PIR B00941), HOX10 mouse (SWISS-PROT P31257), HOX10 chick (SWISS-PROT P24341), HOX10 human (SWISS-PROT P28358), HOX10 human (SWISS-PROT P28359).


HOX12 HOX12 human (SWISS-PROT P31275), HOX12 mouse (SWISS-PROT P31315), HOX12 chick (SWISS-PROT P24343), HOX12 mouse (SWISS-PROT P28312), HOX12 human (PIR C30065).


*HOX1-13 represent paralogous groups.*

Changes in HOX characteristic residues lead to the acquisition of new functions.

Defining characteristic residues of *Hox* paralogs inside the homeodomain

Consensus sequences for *Hox* paralogous groups were determined using vertebrate, fly and *Amphioxus* HD sequences (Fig. 1; see Box 1 for sources of sequences). Only positions common to all the sequences of each paralog group are given in the final HOX consensus sequence (lower line in each group). For most of the paralog groups a clear consensus can be defined; the most conserved residues are the same in other paralog groups.

Using the consensus sequences defined in Fig. 1, we searched within the paralogous consensus sequences for "characteristic residues". The number, position and nature of characteristic residues (summarized in red letters in Fig. 2) distinguish most paralog groups from one another. Paralog groups 1, 2, 3, 10 and 13 have a large number of characteristic residues (3 to 12); HOX groups 4, 7, 8, 11 and 12 each have a single distinguishing residue that defines the group. HOX5, 6 and 9 paralog groups cannot be distinguished from one another based solely on their HDs. The gray highlighting indicates framework residues common to all the HDs.

Projection of characteristic residues on the HD-DNA interaction model

The NMR or X-ray crystal structures of the HDs of several HD proteins have been determined (Refs 23–26;
TABLE 2

<table>
<thead>
<tr>
<th>Consensus</th>
<th>Helix 1</th>
<th>Helix 2</th>
<th>Helix 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 20 30 40 50 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOX1</td>
<td>KF Q LE E A LE NQ MP QRRR OR R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOX2</td>
<td>L QT LE E CP N L Q MP QRRR RP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOX3</td>
<td>KV LE E V L Q MP QRRR VK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOX4</td>
<td>A Q LE E V L Q MP QRRR K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOX5</td>
<td>Q LE E L Q MP QRRR K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOX6</td>
<td>Q LE E L Q MP QRRR K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOX7</td>
<td>K Q LE E L Q MP QRRR K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOX8</td>
<td>Q LE E L Q MP QRRR K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOX9</td>
<td>Q LE E L Q MP QRRR K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOX10</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HOX11</td>
<td>Q LE E L L Q MP QRRR K</td>
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<td></td>
</tr>
<tr>
<td>HOX12</td>
<td>Q LE E L L Q MP QRRR K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOX13</td>
<td>V Q LE ETA F K K RR LE Q T MP QRRR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Characteristic residues outside the homeodomain**

Extended sequence conservation near the HD, on both N- and C-terminal sides, provides useful additional criteria for paralog grouping. The available sequences extend as far as 100 residues on either side of the HD, but conservation is limited to sequences close to the HD. The pattern of conservation and characteristic residues are shown in Fig. 4 (see also Ref. 22).

Within the HOX1, 2, 3, 12 and 13 paralog groups, little or no similarity is observed outside the HD. HOX1 and HOX3 have only one characteristic residue each, while HOX2, 12 and 13 have none. All other paralog groups have significant conservation and characteristic residues outside the HD. HOX9 and 10 proteins have conserved characteristic residues within eight amino acids just upstream of the HD. HOX10 and 11 proteins have long stretches of characteristic residues C-terminal to the HD. N-terminal to the HD, most HOX proteins, except HOX1 paralogs 2 and 9–13, have in common a conserved hexapeptide motif presumably involved in the interaction with HOX-assisting cofactors. Within paralog groups 1 and 3 not all members have a hexapeptide motif and, when it is present, its position relative to the HD is variable. In contrast, members of HOX paralog groups 4–8 all share the motif in constant position for each paralog group. For these groups, the motif, as well as some residues flanking the motif or scattered some distance away, provide HOX-paralog-specific characteristics.

HOX classes with one (or no) characteristic residue inside the HD have many in the regions adjacent to the HD. In contrast HOX1, 2, 3 and 13 proteins have a large number of characteristic residues inside the HD, but few or none outside of the HD. In general, sequence comparisons using up to 100 residues outside of the HD reveal clusters of conserved amino acids lying close to the HD. The conserved and characteristic amino acids in HOX9–11 proteins extend the HD, while conserved residues N-terminal to the HD in HOX1–8 probably contribute to the specific function of the hexapeptide motif in each paralog.

**Classifying Hox genes in Caenorhabditis elegans**

The small Hox cluster in the nematode C. elegans consists of four genes. In 3' to 5' order, they are ceh-13, lin-39, mab-5 and egl-5 (Ref. 36). Even though a nonsegmented body sets apart the nematode from insects and vertebrates, genes in the complex specify anterior–posterior position-specific information in the determination of cell fates12. Which HOX paralog characteristics does each nematode HOX protein exhibit, and to what extent do the characteristic residues defined in fly, *Amphioxus* and vertebrate Hox genes extend to nematodes?
CEH-13 possesses many of the distinguishing features of the HOX1 class. HOX1 has seven characteristic residues inside the HD, three of which are shared by CEH-13 (Fig. 5). In addition to these, CEH-13 protein has two amino acids, at positions 61 and 62 just C-terminal to the HD, which are the same in Amphioxus HOX1 and fly labial. The vertebrate HOX1 consensus sequence also shares the amino acid at position 62 with the CEH-13 protein. These similarities identify CEH-13 as a HOX1 homolog, in agreement with past assignments, but based on different criteria.

The nematode proteins LIN-39 and MAB-5 both have hexapeptides, which places them closest to HOX paralog groups 4–8. These paralog groups have one or zero characteristic residues within the HD, so sequences flanking the hexapeptide sequence must be considered. LIN-39 has two residues near the so called 'hexapeptide' that are characteristic for the vertebrate HOX4 class: a valine directly on the N-terminal side of the YPWM motif and a histidine four residues on the C-terminal side. In addition, LIN-39 shares the one characteristic HD residue of the Drosophila-Amphioxus-vertebrate paralog 4 group. Thus, characteristic residues inside and outside the HD classify LIN-39 as a HOX4 paralog.

The hexapeptide of MAB-5 protein is YPWM, like vertebrate HOX8 and Amphioxus HOX6. Two of the residues directly N-terminal to the MAB-5 HD are also found in Amphioxus HOX6. Inside the HD, however, MAB-5 has the one characteristic residue of the paralog 8 group. HOX6 has no characteristic HD residues, so only the conserved sequence around the hexapeptide and just outside of the HD can be used to distinguish it from other paralogs. Because MAB-5 exhibits some features of HOX6 and HOX8, MAB-5 cannot be definitively placed as a homolog of either paralog group.

EGL-5 protein has significant similarity to the Drosophila homeotic protein abdominal B (ABD-B), both within the HD and directly N-terminal and C-terminal to it. Although the HOX9 Drosophila-Amphioxus-vertebrate consensus has no characteristic residue in the HD, EGL-5 is very similar to ABD-B, Amphioxus HOX9 and Amphioxus HOX10. EGL-5 shares no characteristic residues with the HOX10–13 consensus sequences. N-terminal to the HD, EGL-5 has two residues shared by vertebrates and flies, and C-terminal to the HD EGL-5 has two identities with ABD-B (Fig. 5) and two with Amphioxus HOX9. Although EGL-5 is more like the HOX9 Drosophila-Amphioxus-vertebrate consensus than like the consensus of any other paralog group, EGL-5 is closer to the fly protein ABD-B and Amphioxus HOX9 and 10 than to the vertebrate HOX9 consensus sequence.

Classifying HoX genes in the sea urchin

Sea urchins have a distinctive body plan that makes them particularly interesting for examining the evolution of HOX genes. Although little has been described about expression patterns, some sea urchin HOX HD sequences have been published and placed in categories. We have applied characteristic residue criteria to the analysis of these sea urchin sequences.
**Figure 4.** Conserved and paralog characteristic residues outside the homeodomain (HD). The position of the HD is represented by a gray rectangle. Red bars symbolize characteristic residues within the HD (refer to Fig. 2). Amino acids represented in black or red are conserved by vertebrate members of the paralog group. Red residues are characteristic of paralogs among the vertebrate sequences. Characteristic residues that are conserved by *Drosophila* as well as vertebrate sequences are highlighted in yellow. *Amphioxus* sequences are not included in this set of comparisons because most available *Amphioxus* sequences do not extend far enough beyond the HD. Positions are numbered relative to the HD. The so-called 'hexapeptide' motif, when shared in constant position by all members of a paralog group and when present within the 25 amino acids preceding the HD, are outlined in black.

HeHbox1 cannot be unequivocally placed into a paralog group, but it has one of the three characteristic residues of HOX3 inside the HD (tyrosine at 56) and one of the conserved residues C-terminal to the HD (a lysine three residues C-terminal to the HD). It also has the only HOX7 characteristic residue inside the HD, and one of the conserved residues in the C terminus (a lysine directly C-terminal to the HD). The available sequence extends only eight residues upstream of the HD and there is no hexapeptide within this region. Therefore, HeHbox1 cannot be definitively placed into a paralog group until more sequence information becomes available. HeHbox6 is most like HOX7. This assignment is tentative, pending additional sequence N-terminal to the HD. HeHbox6 has the one characteristic HOX7 residue inside the HD (lysine at position 2) and two of the residues conserved by HOX7 N-terminal to the HD (glycine-asparagine directly preceding the HD). Popoch et al. found HeHbox7 to be ABD-B-like (i.e., HOX9-13), but based on characteristic residues it appears to be most related to HOX8. It has the one characteristic serine at position 9 inside the HD and two of the five characteristic residues in the C-terminal region (two lysines at positions 2 and 4 C-terminal to the HD). The published sequence extends 15 residues N-terminal to the HD, but there is no hexapeptide sequence, whereas the HOX8 hexapeptide sequence is usually found 6-11 amino acids N-terminal to the HD. HeHbox9 has the single HOX4 characteristic residue inside the HD (alanine at position 7). The C-terminal region does not match any of the HOX classes. Tentatively HeHbox9 might be HOX4-like, but the unreported upstream sequence might include a hexapeptide that would help in the assignment. Finally, HeHbox10 makes a good match with the HOX10 class. It has three out of four of the characteristic residues inside the HD. It is not a perfect match, lacking the conserved residues C-terminal to the HD and having at position 1 a threonine rather than the expected glycine.

**Conclusions**

*Hox* genes are highly related in sequence, but act very specifically in their roles in pattern formation and development. In this study, we define residues distinguishing HOX paralog groups from one another. HOX classes with one or no characteristic residue inside the HD have a significant number of characteristic residues outside the HD. All paralog groups are distinguishable when characteristic residues inside and outside the HD are considered, although some groups have more characteristic features than others. We tested the usefulness of characteristic residues as a tool for classifying HOX proteins by using them to re-examine the classification of the distantly related nematode HOX cluster gene products. The nematode HOX proteins have more extensive similarity to corresponding *Drosophila* and *Amphioxus* proteins than to the vertebrate consensus sequences. Of the *C. elegans* HOX genes, three could be clearly related to *Hox* paralog groups, but *mab-5* cannot be definitively classified because it exhibits characteristics of *Hox6* and *Hox8*. This example illustrates how characteristic residues can be used for HOX paralog classification purposes and indicates that this criterion should be an additional helpful tool as new HOX genes are in need of paralog group assignment.

An important conclusion of this study is that characteristic residues are likely to be involved in protein–protein interactions. Within the HD, characteristic residues are primarily located on surfaces oriented away from the DNA. C-terminal to the HD, characteristic residues extend the HD (HOX9-11), while characteristic residues N-terminal to it in HOX1–8 probably contribute to the specific function of the hexapeptide motif in each paralog, perhaps by working with the extradenticle (EXD)/PBX family of proteins. The EXD–HOX protein contacts are not fully known, but amino acids within the HD and sequences N-terminal to the HD, including the hexapeptide motif, have been found to be necessary. These contact sites are reminiscent of contacts in protein complexes assembled to regulate yeast mating type. In conclusion, while few HOX or HD protein–cofactor complexes have been analysed to date, our study suggests that protein–protein interaction is a widely used strategy for conferring specificity on HOX proteins.
The analyses of conservation of Hox genes over great evolutionary spans, to worms and sea urchins for example, indicate that characteristic residues might be useful for organisms that are not closely related either to mammals or to insects. However, the results also emphasize that characteristic residues are not universal—over large evolutionary distances they change. We suggest that these changes are especially significant because they might indicate important alterations in the functions of the proteins, such as gain or loss of the ability to interact with particular cofactors. In this view, when characteristic residues are not found in their accustomed positions, the gene has, in fact, changed meaningfully in its function and cannot be equated with any particular gene in a distantly related organism.

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