Homeoboksit ja homeodomain

Tarkastelemalla yhden *säätelygeeniperheen* fylogeniaa saamme yhden valaisevan näkökulman siihen, miten evoluutio on monimutkaistanut eliöitä sattumanvaraisten mutaatioiden ja niitä "jalostavan" luonnonvalinnan kautta

ing: “if it could be demonstrated that any complex organ existed which could not possibly have been formed by numerous, successive, slight modifications, my theory would absolutely break down.”

Darwin

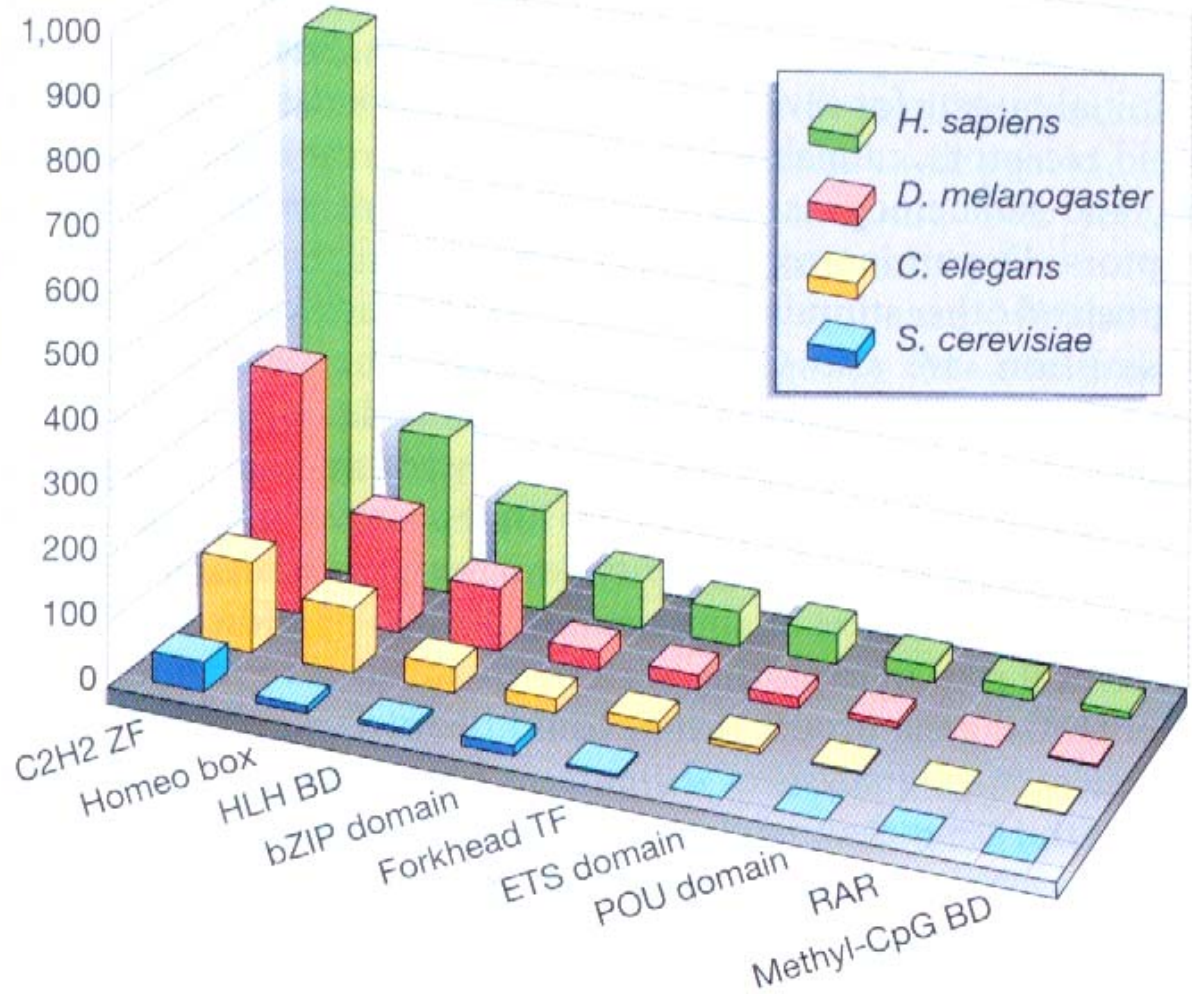


Figure 1 Genome-wide comparison of transcriptional activator families in eukaryotes. The relative sizes of transcriptional activator families among *Homo sapiens, D. melanogaster, C. elegans and S. cerevisiae* are indicated, derived from an analysis of eukaryotic proteomes using the INTERPRO database, which incorporates Pfam, PRINTS and Prosite. The transcription factors families shown are the largest of their category out of the 1,502 human protein families listed by the IPI.

Homeoboksin sisältävät geenit ovat **sinkkisormien** jälkeen yleisimmät transkription säätelijät kaikilla *eläimillä*

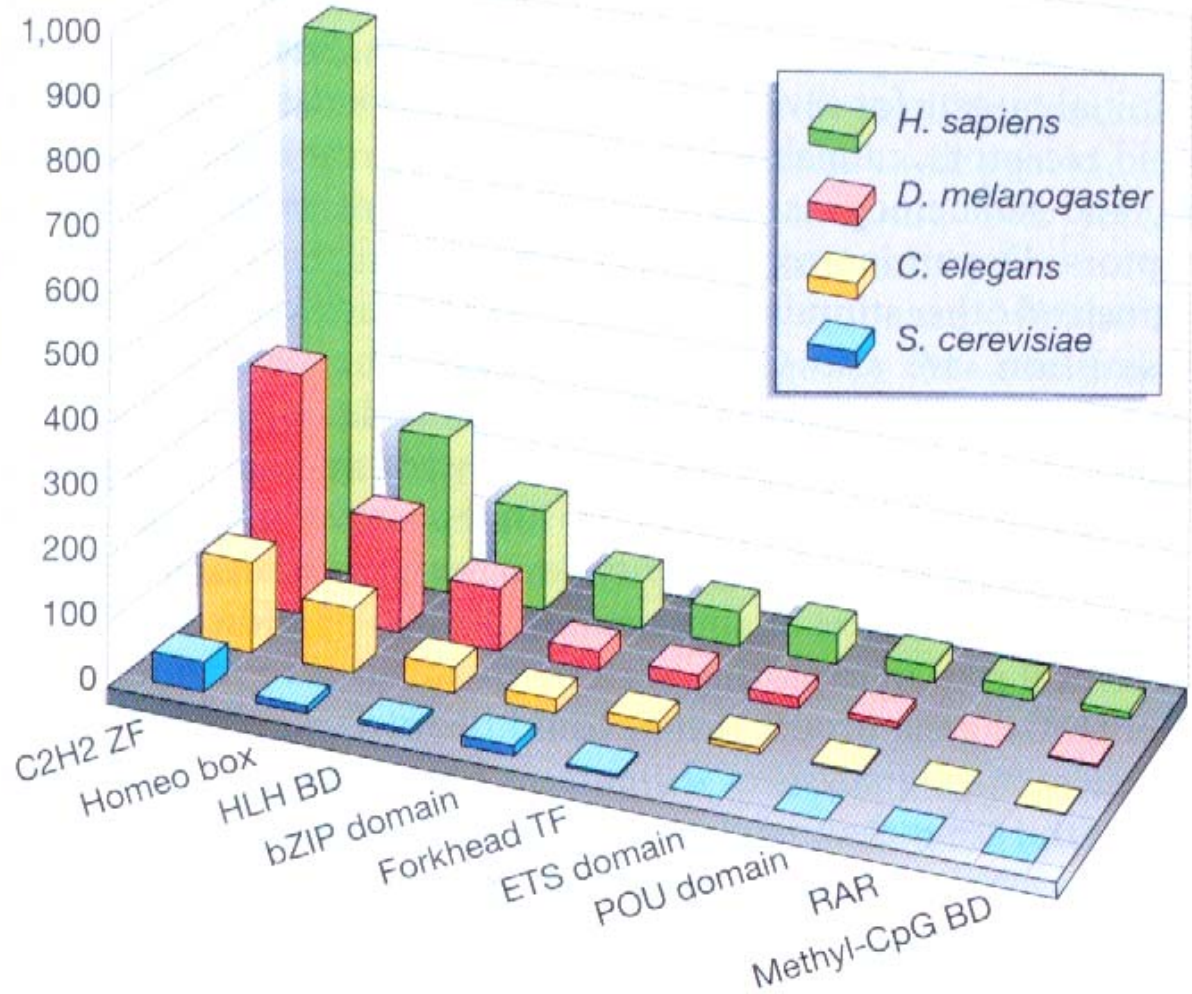


Figure 1 Genome-wide comparison of transcriptional activator families in eukaryotes. The relative sizes of transcriptional activator families among *Homo sapiens, D. melanogaster, C. elegans and S. cerevisiae* are indicated, derived from an analysis of eukaryotic proteomes using the INTERPRO database, which incorporates Pfam, PRINTS and Prosite. The transcription factors families shown are the largest of their category out of the 1,502 human protein families listed by the IPI.

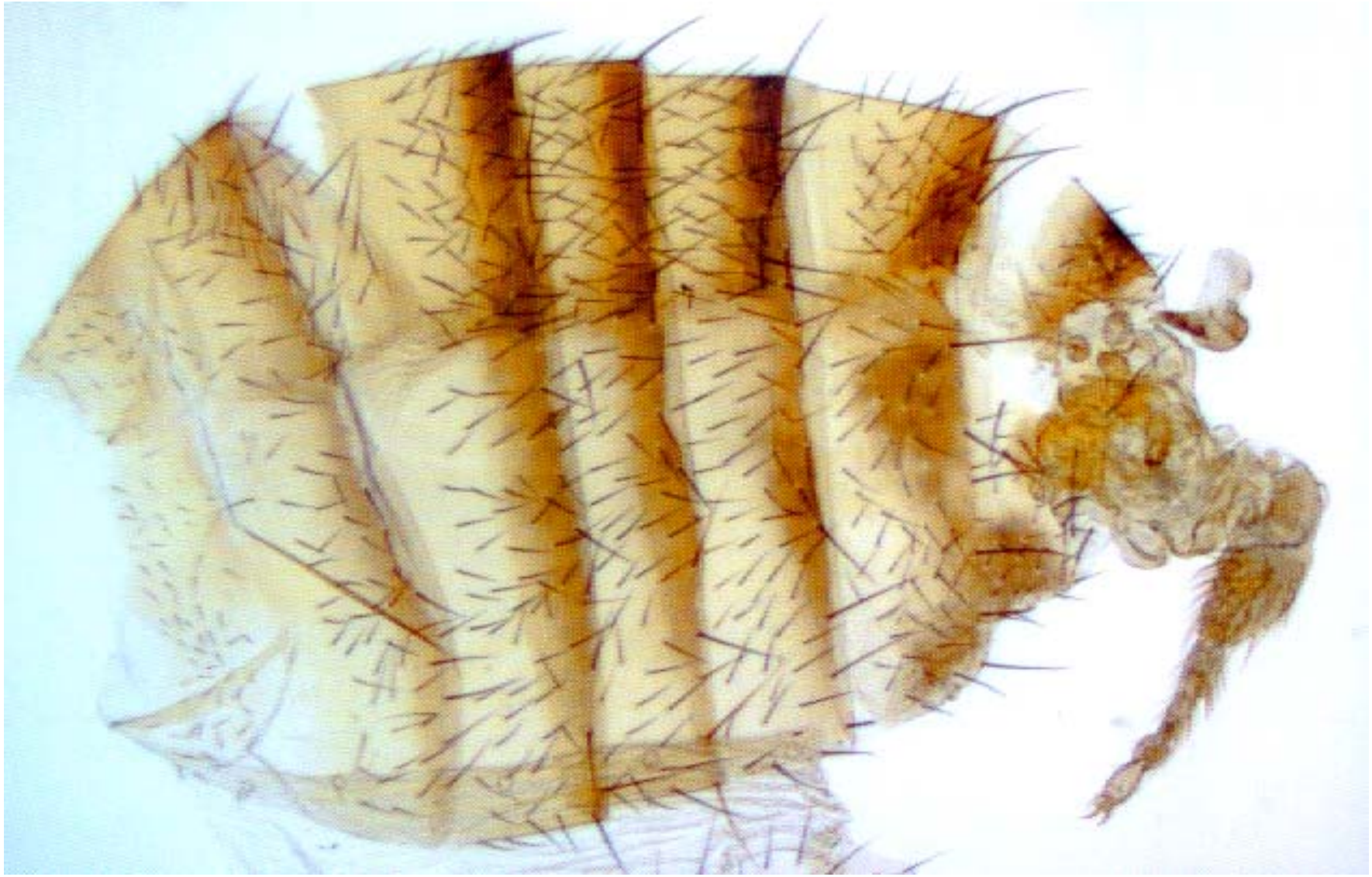
Homeoboksit

toiseksi yleisin luokka meillä ihmisillä;

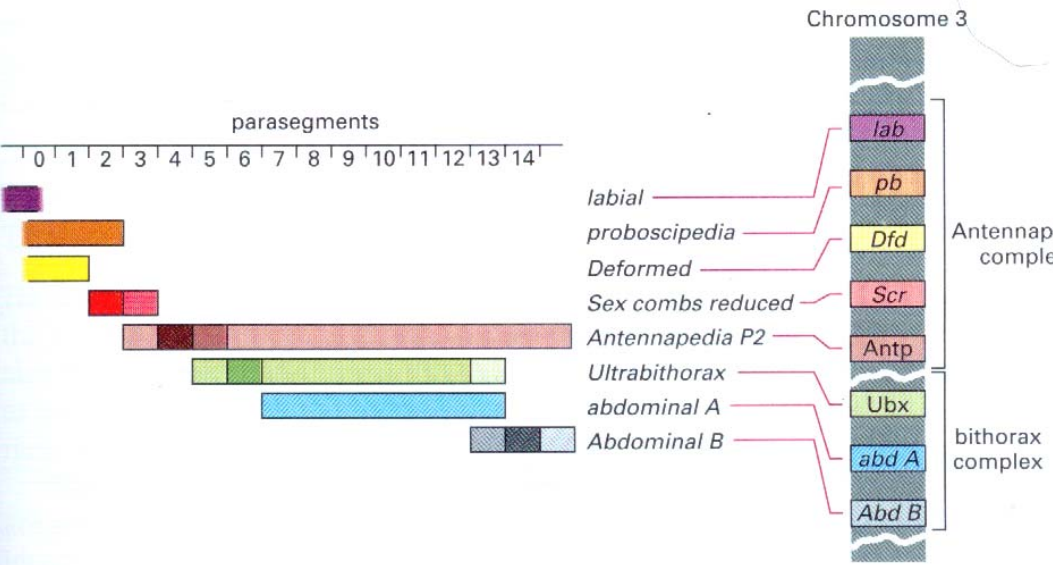
niistä lisää kehitysgenetiikan puolella

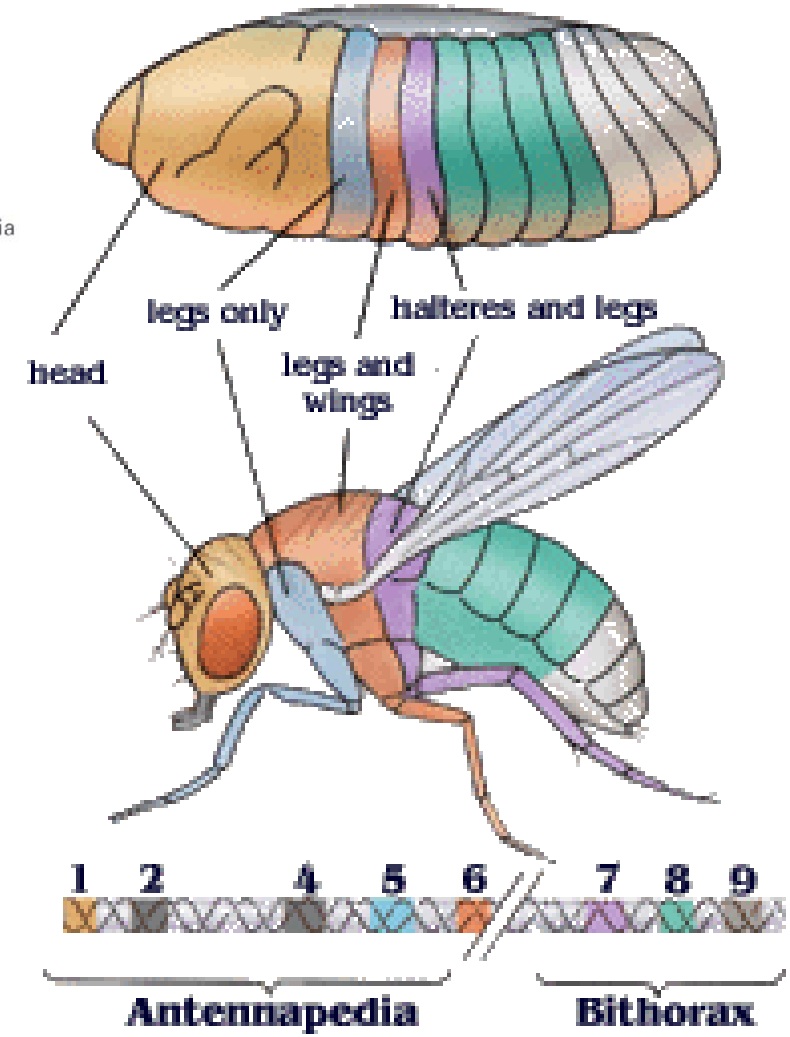
Ed Lewisin juhlanäyte: kaksoismutantti *bithorax-postbithorax*

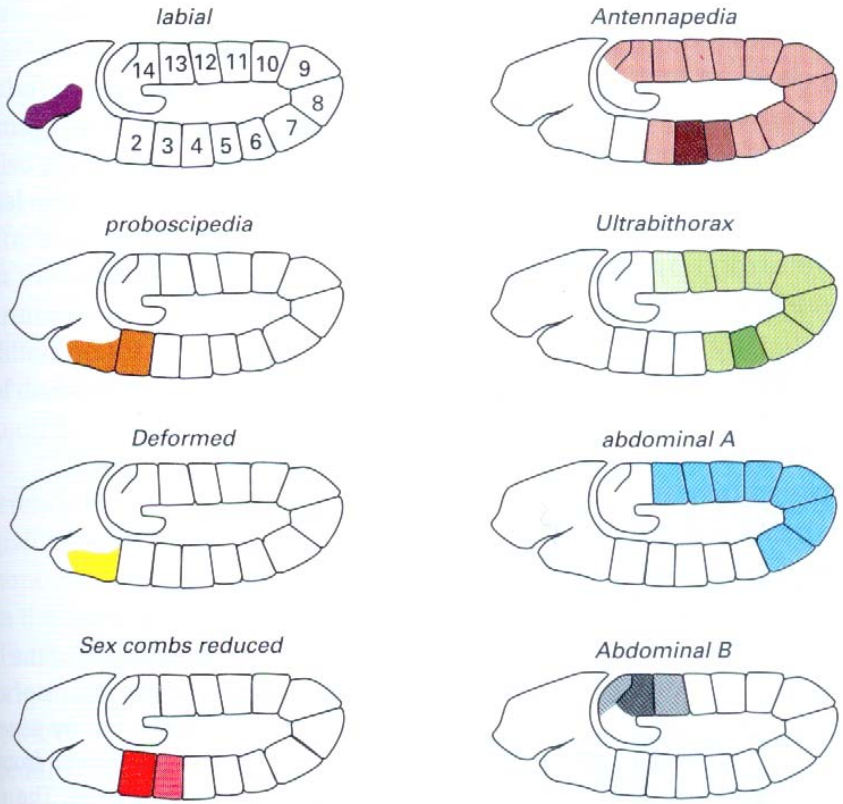
Antennapedia



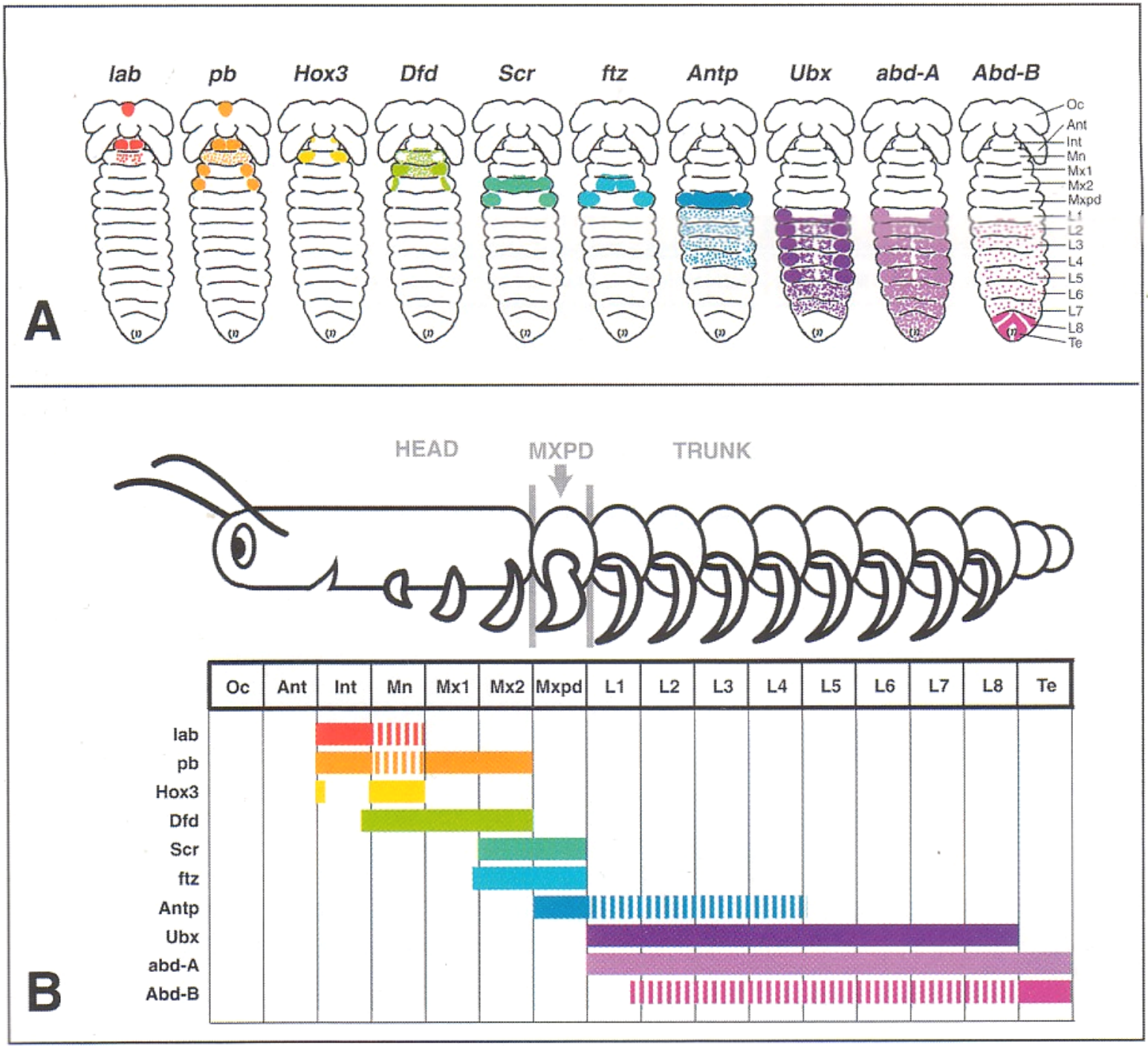
abdominal-B on homeoottinen geeni, mutantilla jalka genitaalien paikalla







Kaikista näistä geeneistä jotka viallisena aiheuttivat oikeita elimiä väärissä paikoissa löytyi **homeoboksi**



Satajalkaisen (Centipede) Hox

Development March 2002 p. 1225-

Hämähäkit
Äyriäiset
Myriapodit
Hyönteiset
samassa vihkossa

Homeodomain (aminohappojakso)
Homeoboksi (tunnistettava nukleotidisekvenssi)

ovat homeoottisten selektoriproteiinin (-geenin) osia

Homeoottiset selektorigeenit säätelevät eläinten kehitystä määräämällä, mitä kustakin alkion alueesta ja jokaisesta solusta tulee ’isona’

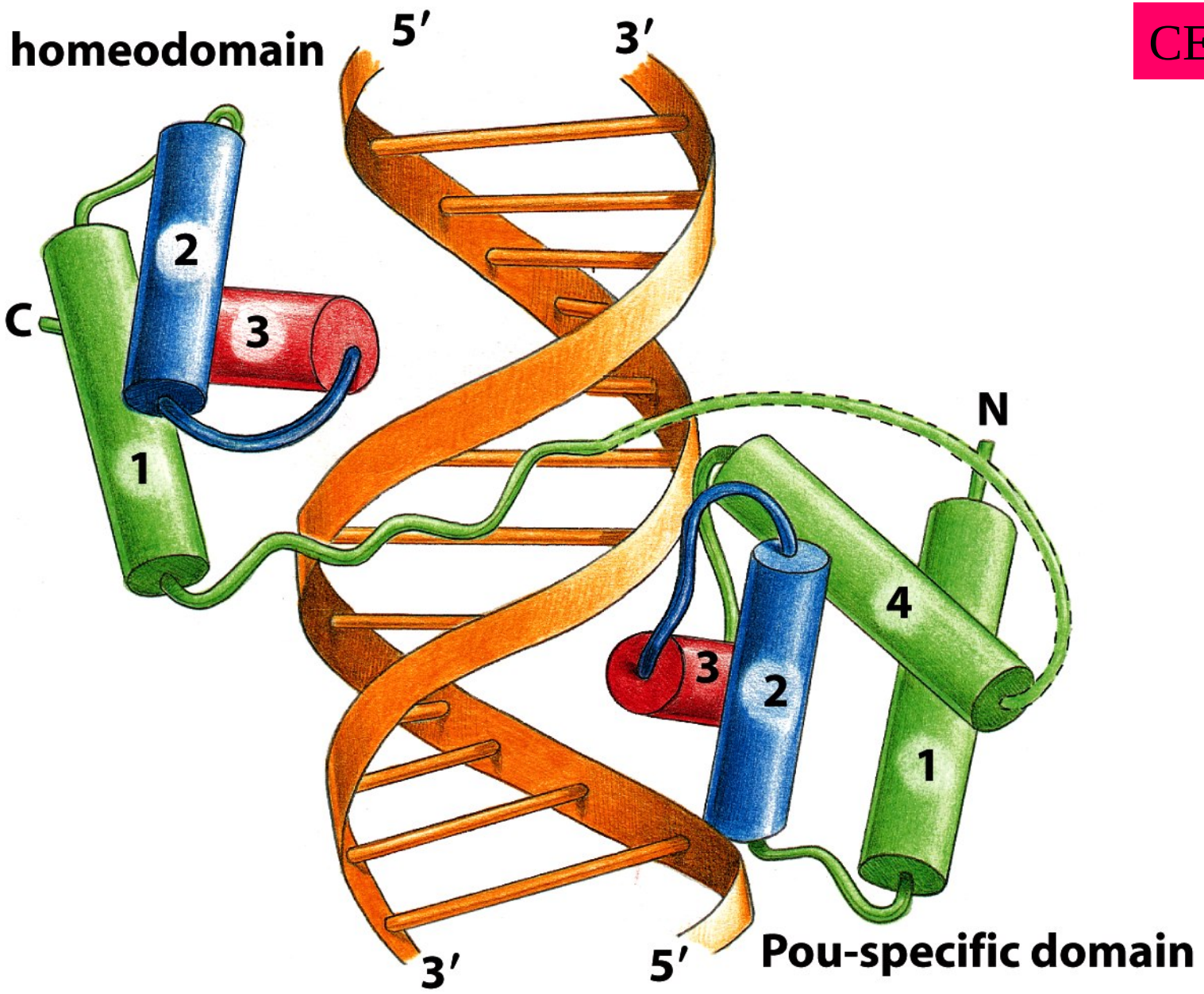


Figure 7-22 Molecular Biology of the Cell 5/e (© Garland Science 2008)

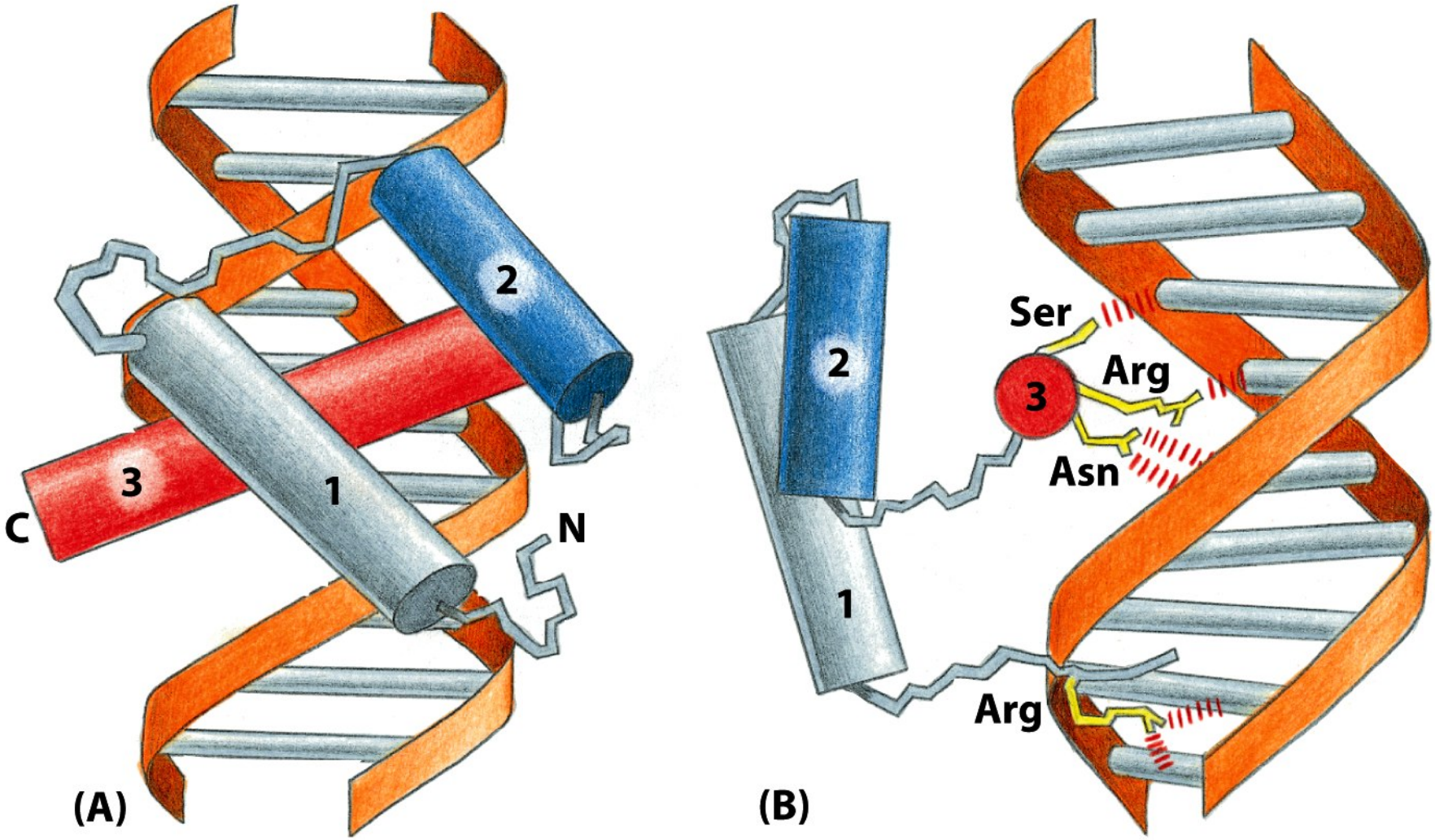


Figure 7-13 Molecular Biology of the Cell 5/e (© Garland Science 2008)

homeodomain sitoutuu spesifiseen sekvenssiin

CELL 421

CELL 425

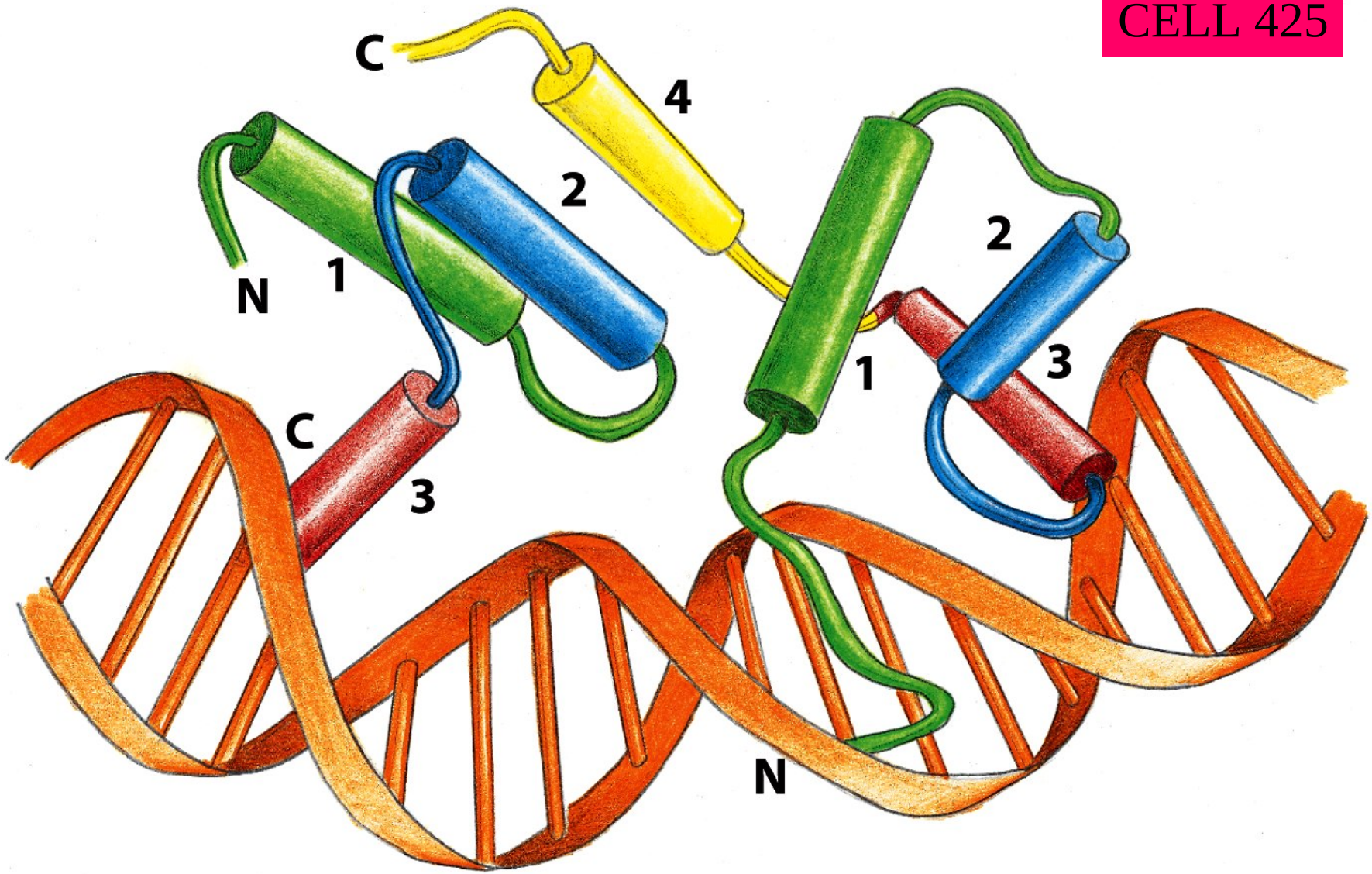
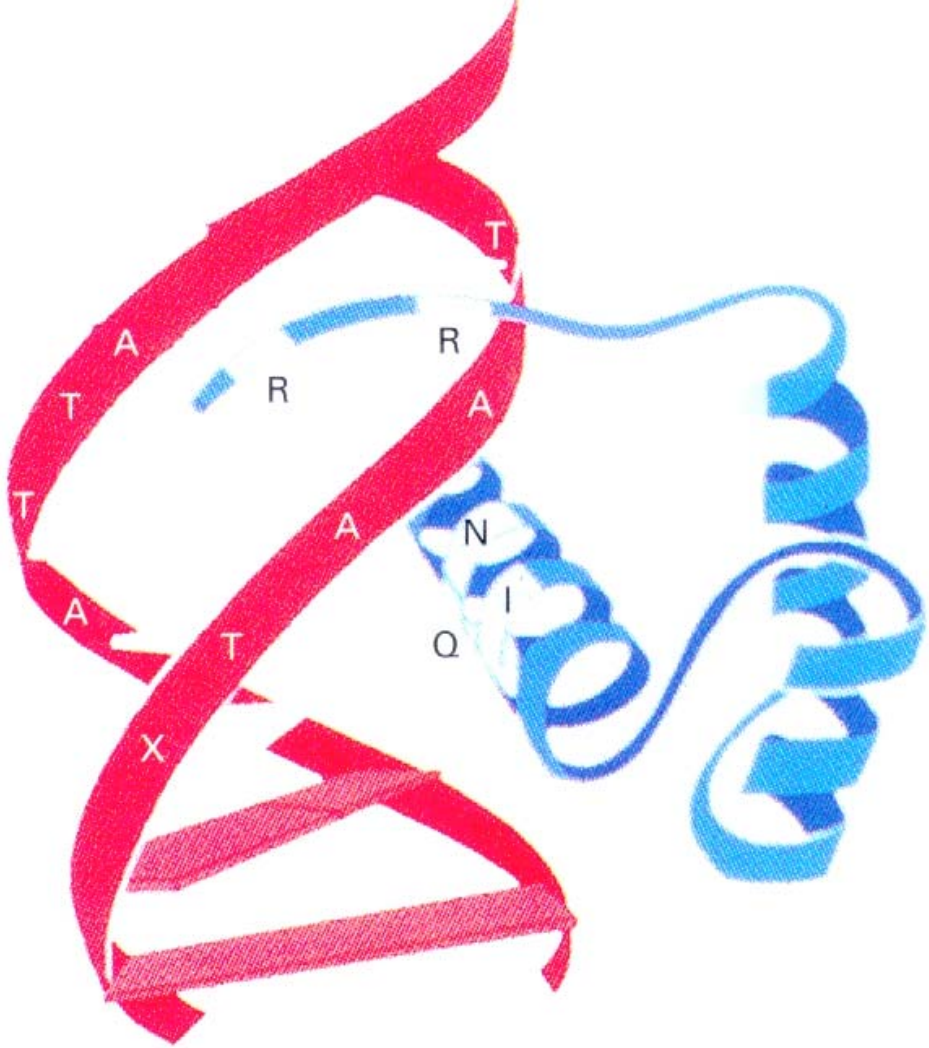


Figure 7-21 Molecular Biology of the Cell 5/e (© Garland Science 2008)

2 homeodomainia heterodimeerinä

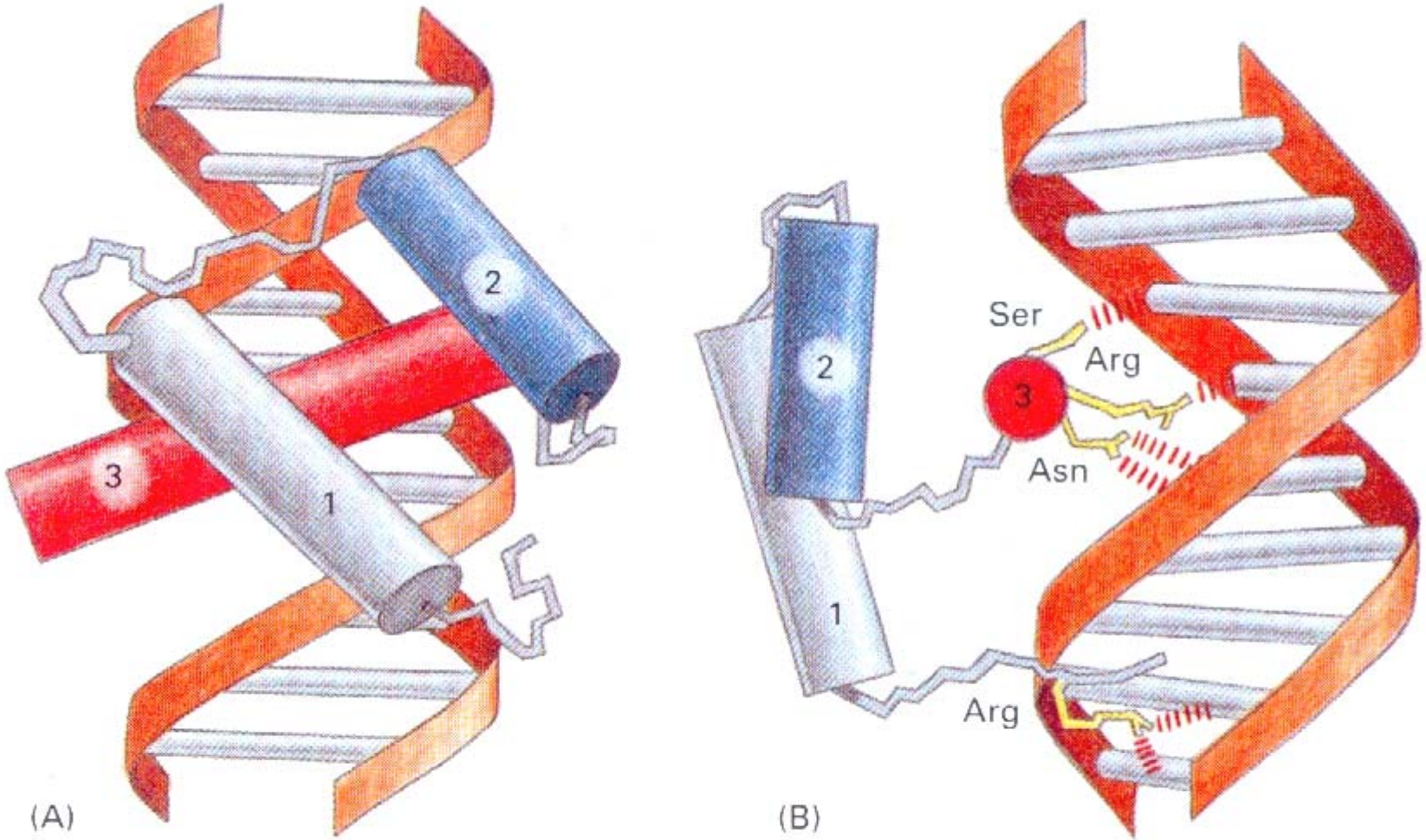


▲ **FIGURE 10-40 Homeodomain from Engrailed protein interacting with its specific DNA recognition site.** The Engrailed transcription factor is expressed during *Drosophila* embryogenesis. Base pairs in the recognition site that directly contact the protein are shown in white type. Lighter regions ir the protein contain residues that contact the major groove. [Adapted from S. C. Harrison, 1991, *Nature* **353**:715.]

Homeodomain-proteiinit ovat **helix-turn-helix** proteiineja, jotka sitoutuvat spesifiseen DNA:n kohtaan, usein

5'TAATAATAATAA
3'ATTATTATTATT

Homeodomain on 60 aa, joten *homeoboksi* on 180 bp (joskus 61/183)

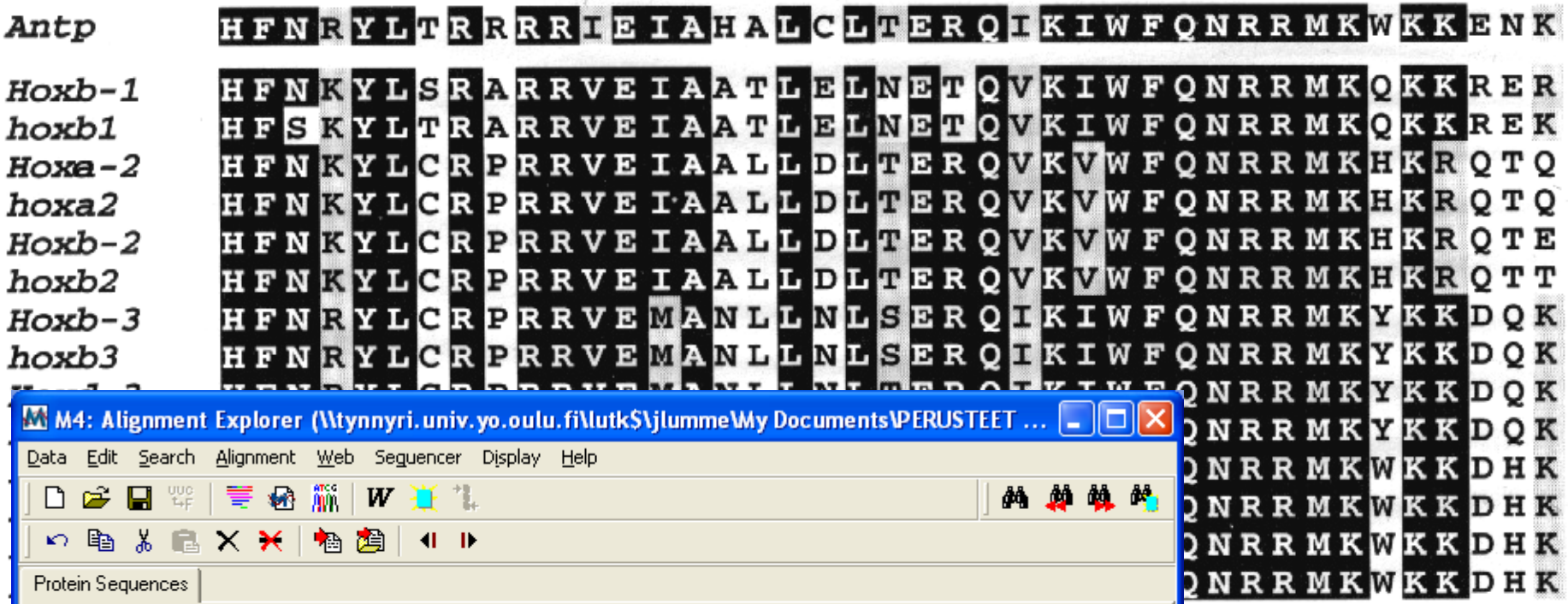


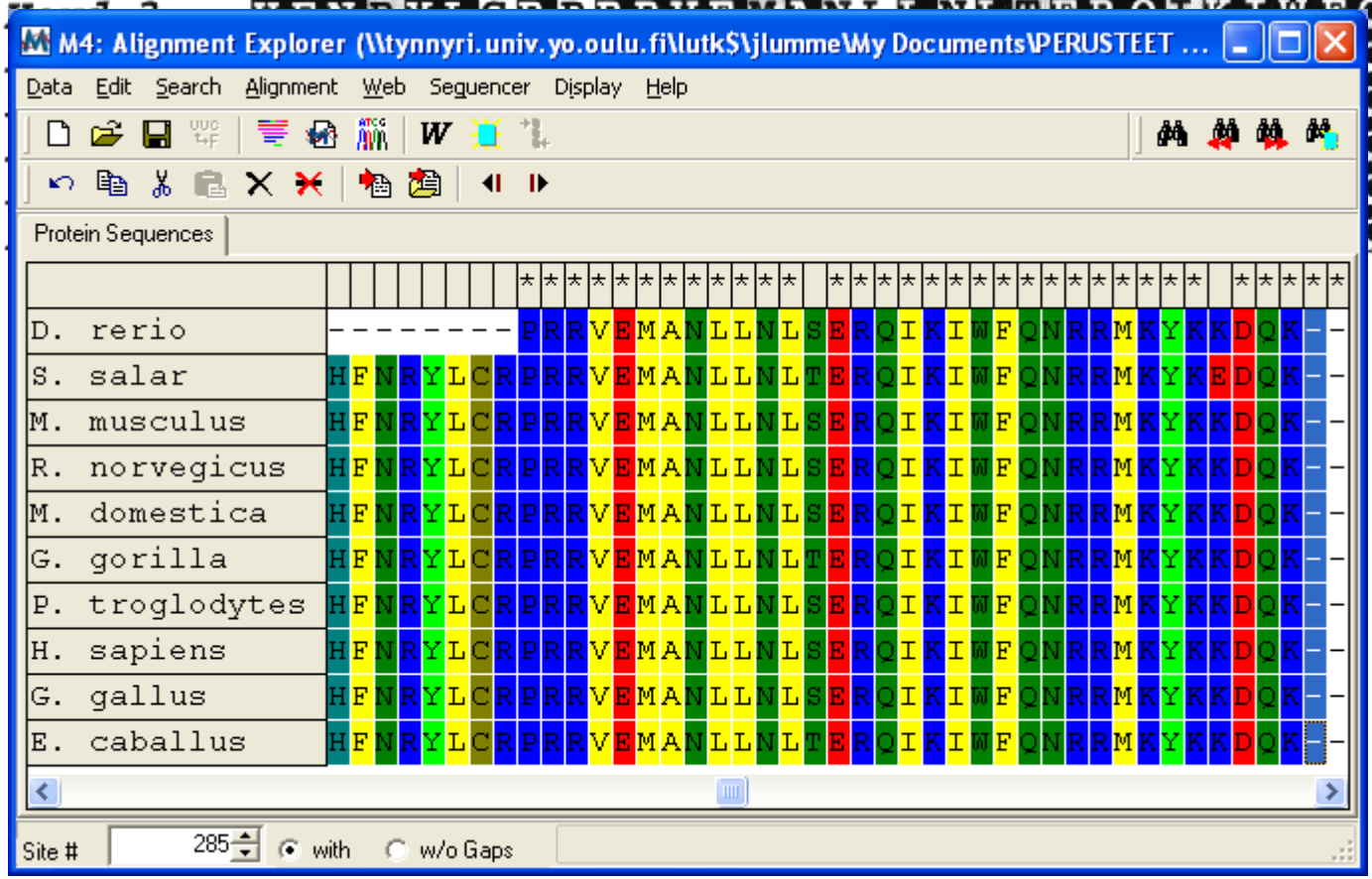
Chapter 9 : Control of Gene Expression

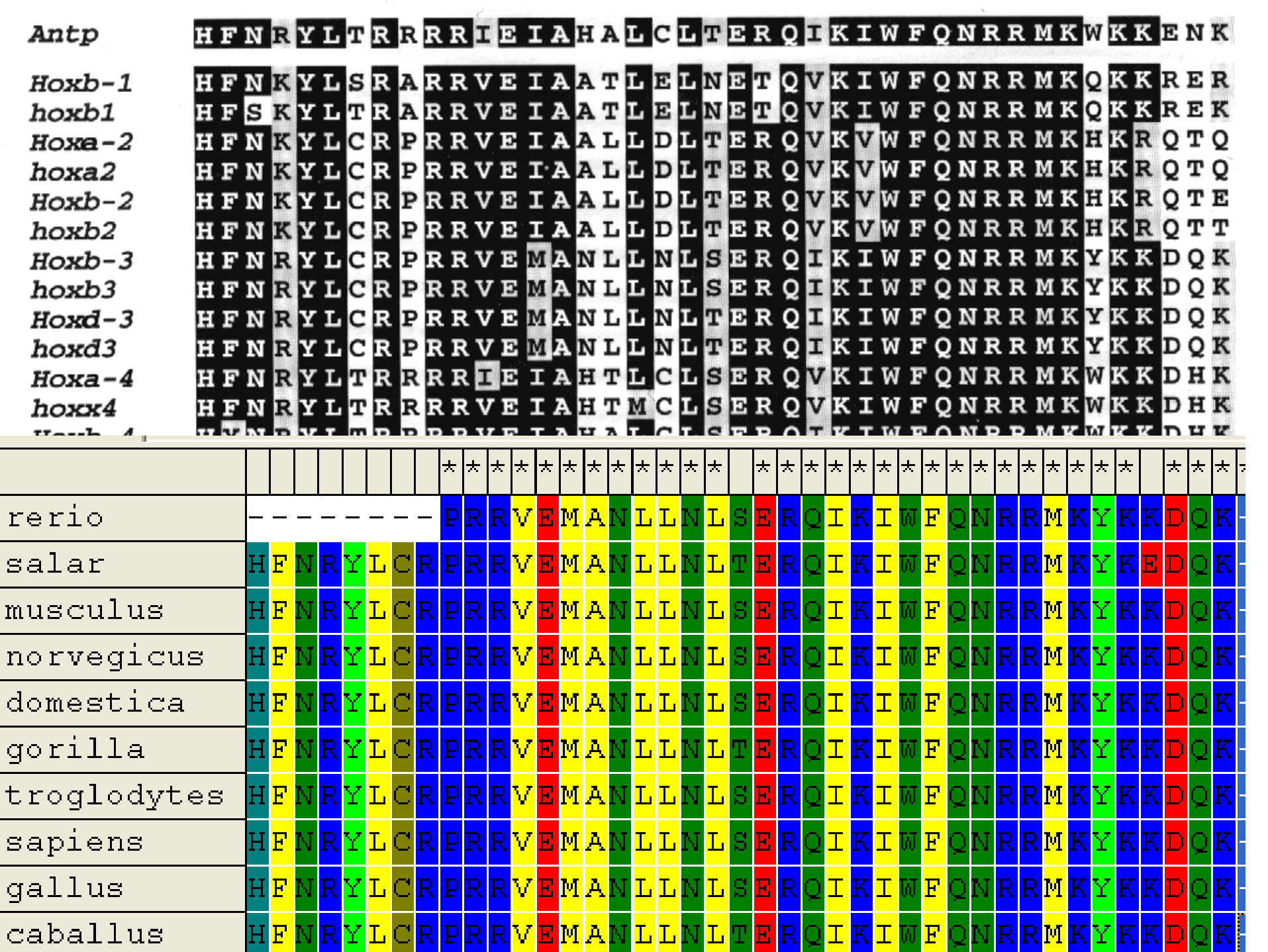
Homeodomain on se *homeoboksin* koodaama motiivi eli aihelma, joka sitten proteiinina tunnistaa ja sitoutuu DNA:n target-sekvenssiin

Fig. 1. Alignments of homeobox sequences for 7 zebrafish *hox* genes with their likely murine *Hox* homologues. In each case the first few amino acids of the zebrafish sequences are taken from Misof et al. (1996; the PCR primers used to clone these cDNAs were based on these sequences). The sequences are compared to the *Drosophila Antennapedia* sequence. Black boxed residues are conserved with *Antp*. All sequences have been submitted to the EMBL database: accession nos Y13944-13950.

Seeprakala (*Danio rerio*) on selkärankaismallina hyvin tykätty. Tässä on ylinnä *Drosophilan Antp* homeobox ja sitten vuorotellen **hiiren** ja **kalan.** Tämä systeemi säätelee etupää-takapää -erilaistumista


Antp HFNRYLTRRRRIEIAHALCLTERQIKIWFQNRRMKWKKENK
Hoxb-1 HFNKYLSRARRVEIAATLELNETQVKIWFQNRRMKQKKRER
hoxb1 HFSKYLTRARRVEIAATLELNETQVKIWFQNRRMKQKKREK
Hoxa-2 HFNKYLCRPRRVEIAALLDLTERQVKVWFQNRRMKHKRQTQ
hoxa2 HFNKYLCRPRRVEIAALLDLTERQVKVWFQNRRMKHKRQTQ
Hoxb-2 HFNKYLCRPRRVEIAALLDLTERQVKVWFQNRRMKHKRQTE
hoxb2 HFNKYLCRPRRVEIAALLDLTERQVKVWFQNRRMKHKRQTT
Hoxb-3 HFNRYLCRPRRVEMANLLNLSERQIKIWFQNRRMKYKKDQK
hoxb3 HFNRYLCRPRRVEMANLLNLSERQIKIWFQNRRMKYKKDQK

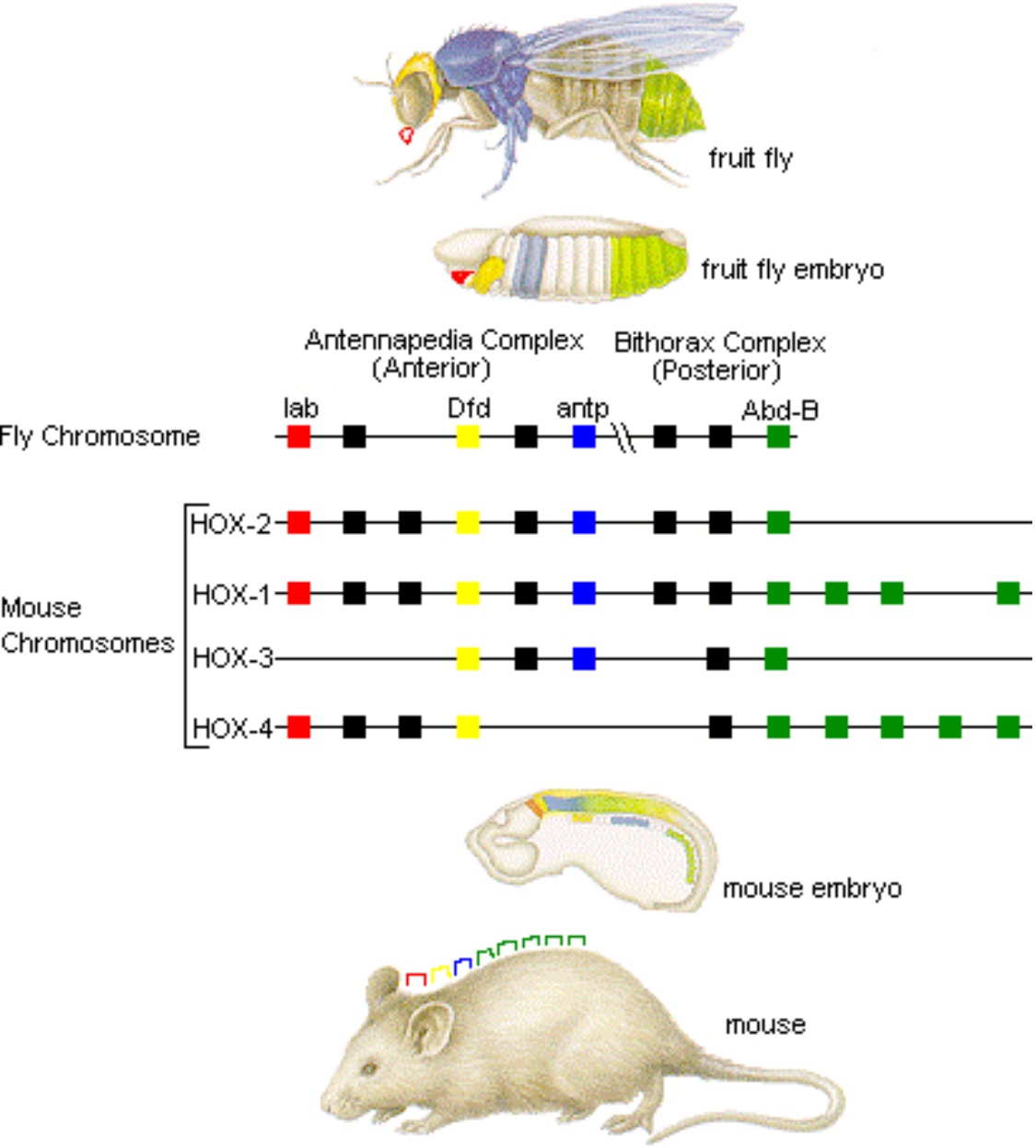

M4: Alignment Explorer (\\tynnyri.univ.yo.oulu.fi\lutk$\jlumme\My Documents\PERUSTEET ...
Data Edit Search Alignment Web Sequencer Display Help
Protein Sequences
D. rerio
S. salar
M. musculus
R. norvegicus
M. domestica
G. gorilla
P. troglodytes
H. sapiens
G. gallus
E. caballus
Site # 285 with w/o Gaps


Antp HFNRYLTRRRRIEIAHALCLTERQIKIWFQNRRMKWKKENK
Hoxb-1 HFNKYLSRARRVEIAATLELNETQVKIWFQNRRMKQKKRER
hoxb1 HFSKYLTRARRVEIAATLELNETQVKIWFQNRRMKQKKREK
Hoxa-2 HFNKYLCRPRRVEIAALLDLTERQVKVWFQNRRMKHKRQTQ
hoxa2 HFNKYLCRPRRVEIAALLDLTERQVKVWFQNRRMKHKRQTQ
Hoxb-2 HFNKYLCRPRRVEIAALLDLTERQVKVWFQNRRMKHKRQTE
hoxb2 HFNKYLCRPRRVEIAALLDLTERQVKVWFQNRRMKHKRQTT
Hoxb-3 HFNRYLCRPRRVEMANLLNLSERQIKIWFQNRRMKYKKDQK
hoxb3 HFNRYLCRPRRVEMANLLNLSERQIKIWFQNRRMKYKKDQK
Hoxd-3 HFNRYLCRPRRVEMANLLNLTERQIKIWFQNRRMKYKKDQK
hoxd3 HFNRYLCRPRRVEMANLLNLTERQIKIWFQNRRMKYKKDQK
Hoxa-4 HFNRYLTRRRRIEIAHTLCLSERQVKIWFQNRRMKWKKDHK
hoxx4 HFNRYLTRRRRVEIAHTMCLSERQVKIWFQNRRMKWKKDHK
rerio --------PRRVEMANLLNLSERQIKIWFQNRRMKYKKDQK
salar HFNRYLCRPRRVEMANLLNLTERQIKIWFQNRRMKYKEDQK
musculus HFNRYLCRPRRVEMANLLNLSERQIKIWFQNRRMKYKKDQK
norvegicus HFNRYLCRPRRVEMANLLNLSERQIKIWFQNRRMKYKKDQK
domestica HFNRYLCRPRRVEMANLLNLSERQIKIWFQNRRMKYKKDQK
gorilla HFNRYLCRPRRVEMANLLNLTERQIKIWFQNRRMKYKKDQK
troglodytes HFNRYLCRPRRVEMANLLNLSERQIKIWFQNRRMKYKKDQK
sapiens HFNRYLCRPRRVEMANLLNLSERQIKIWFQNRRMKYKKDQK
gallus HFNRYLCRPRRVEMANLLNLSERQIKIWFQNRRMKYKKDQK
caballus HFNRYLCRPRRVEMANLLNLTERQIKIWFQNRRMKYKKDQK

bithorax*-** ja ***Antennapedia **-**kompleksit ovat vain yksi *Drosophilan* **homeoboksin** sisältävä geeniryhmä.

Sama aihe, **homeoboksi**, löydettiin sitten monista muistakin *kehitykseen* liittyvistä geeneistä: *fushi tarazu*, *even-skipped*, *engrailed*, *bicoid*, vain tuttuja mainitaksemme

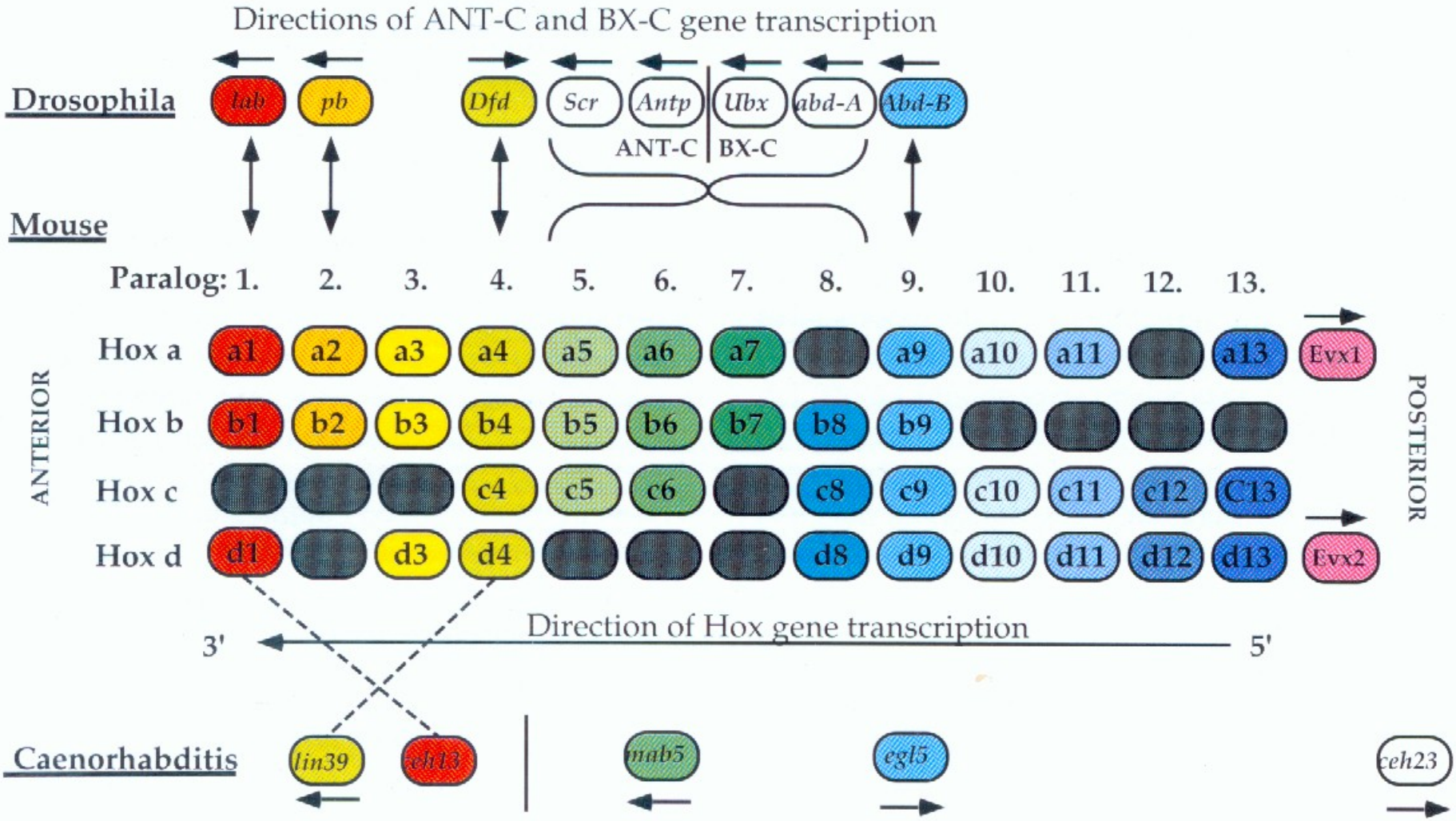
Yhteensä homeobox -geenejä tunnetaan *Drosophilasta* yli sata; 22 ennestään tuntematonta löydettiin vasta koko genomin sekvensoinnissa (Science 24 March 2000)

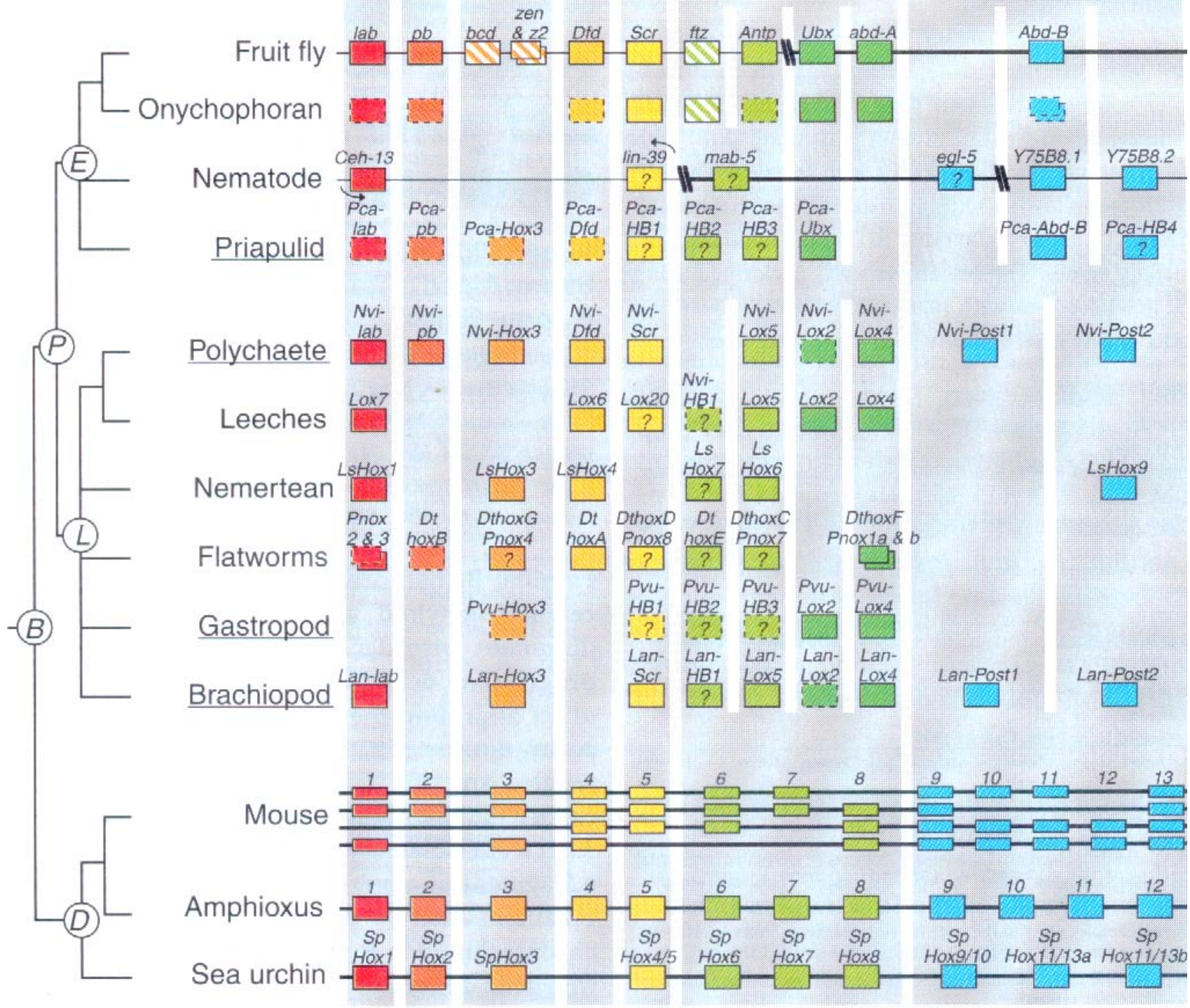


Kun tämä homeoboksi oli tunnistettu, sitä etsittiin muista eliöistä, ja kas kummaa, löytyi. Mutta ei siinä kaikki.

Niistä löytyi koko *Antennapedia-bithorax* -kompleksi, vieläpä useampana kopiona!

The HOX and HOM Complexes




Fruit fly
Onychophoran
Nematode
Priapulid
Polychaete
Leeches
Nemertean
Flatworms
Gastropod
Brachiopod
Mouse
Amphioxus
Sea urchin
E
P
L
B
D
lab
pb
bcd
zen & z2
Dfd
Scr
ftz
Antp
Ubx
abd-A
Abd-B
Ceh-13
lin-39
mab-5
egl-5
Y75B8.1
Y75B8.2
Pca-lab
Pca-pb
Pca-Hox3
Pca-Dfd
Pca-HB1
Pca-HB2
Pca-HB3
Pca-Ubx
Pca-Abd-B
Pca-HB4
Nvi-lab
Nvi-pb
Nvi-Hox3
Nvi-Dfd
Nvi-Scr
Nvi-Lox5
Nvi-Lox2
Nvi-Lox4
Nvi-Post1
Nvi-Post2
Lox7
Lox6
Lox20
Nvi-HB1
Lox5
Lox2
Lox4
LsHox1
LsHox3
LsHox4
Ls Hox7
Ls Hox6
LsHox9
Pnox 2 & 3
Dt hoxB
DthoxG Pnox4
Dt hoxA
DthoxD Pnox8
Dt hoxE
DthoxC Pnox7
DthoxF Pnox1a & b
Pvu-Hox3
Pvu-HB1
Pvu-HB2
Pvu-HB3
Pvu-Lox2
Pvu-Lox4
Lan-lab
Lan-Hox3
Lan-Scr
Lan-HB1
Lan-Lox5
Lan-Lox2
Lan-Lox4
Lan-Post1
Lan-Post2
1
2
3
4
5
6
7
8
9
10
11
12
13
Sp Hox1
Sp Hox2
SpHox3
Sp Hox4/5
Sp Hox6
Sp Hox7
Sp Hox8
Sp Hox9/10
Sp Hox11/13a
Sp Hox11/13b

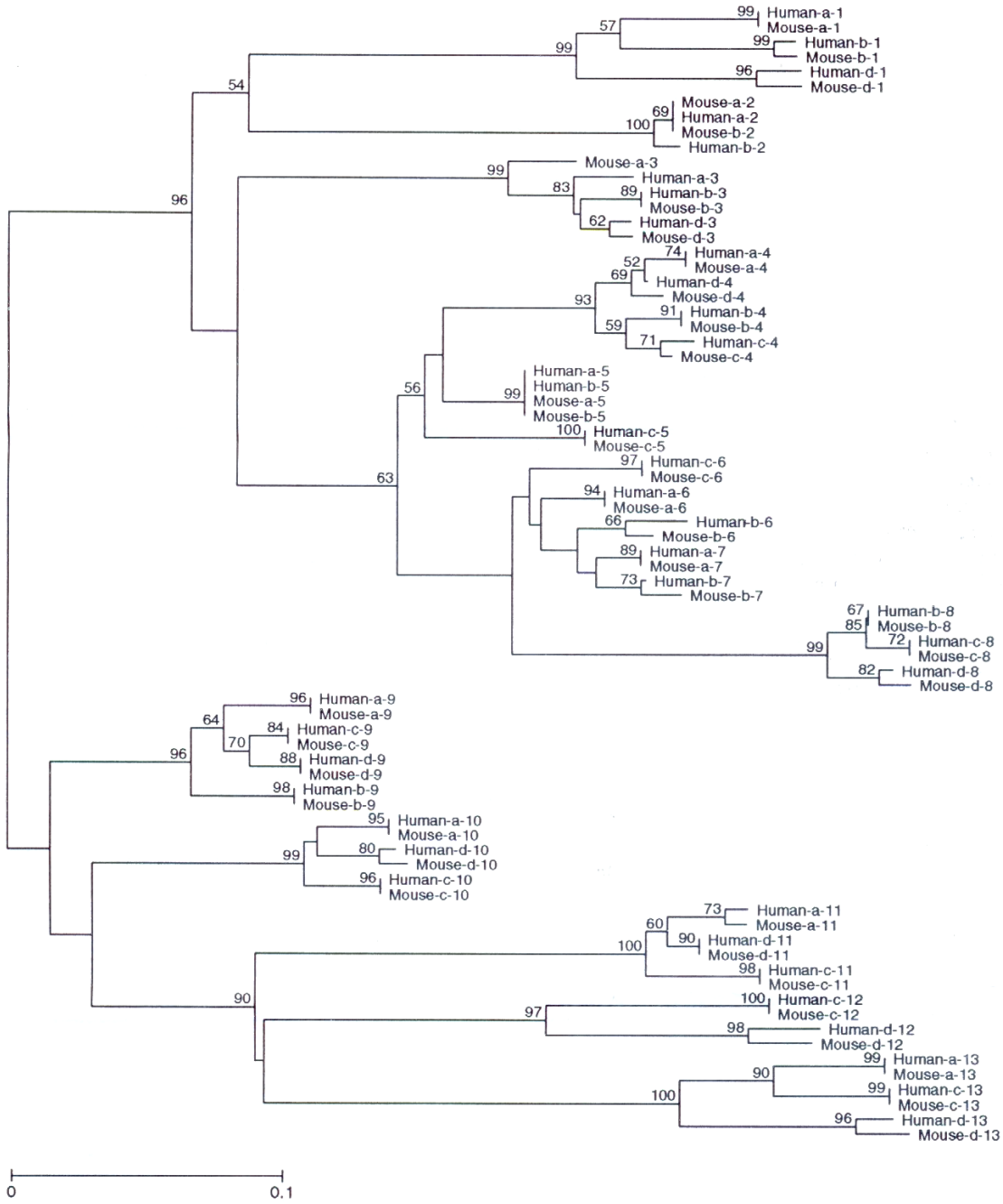


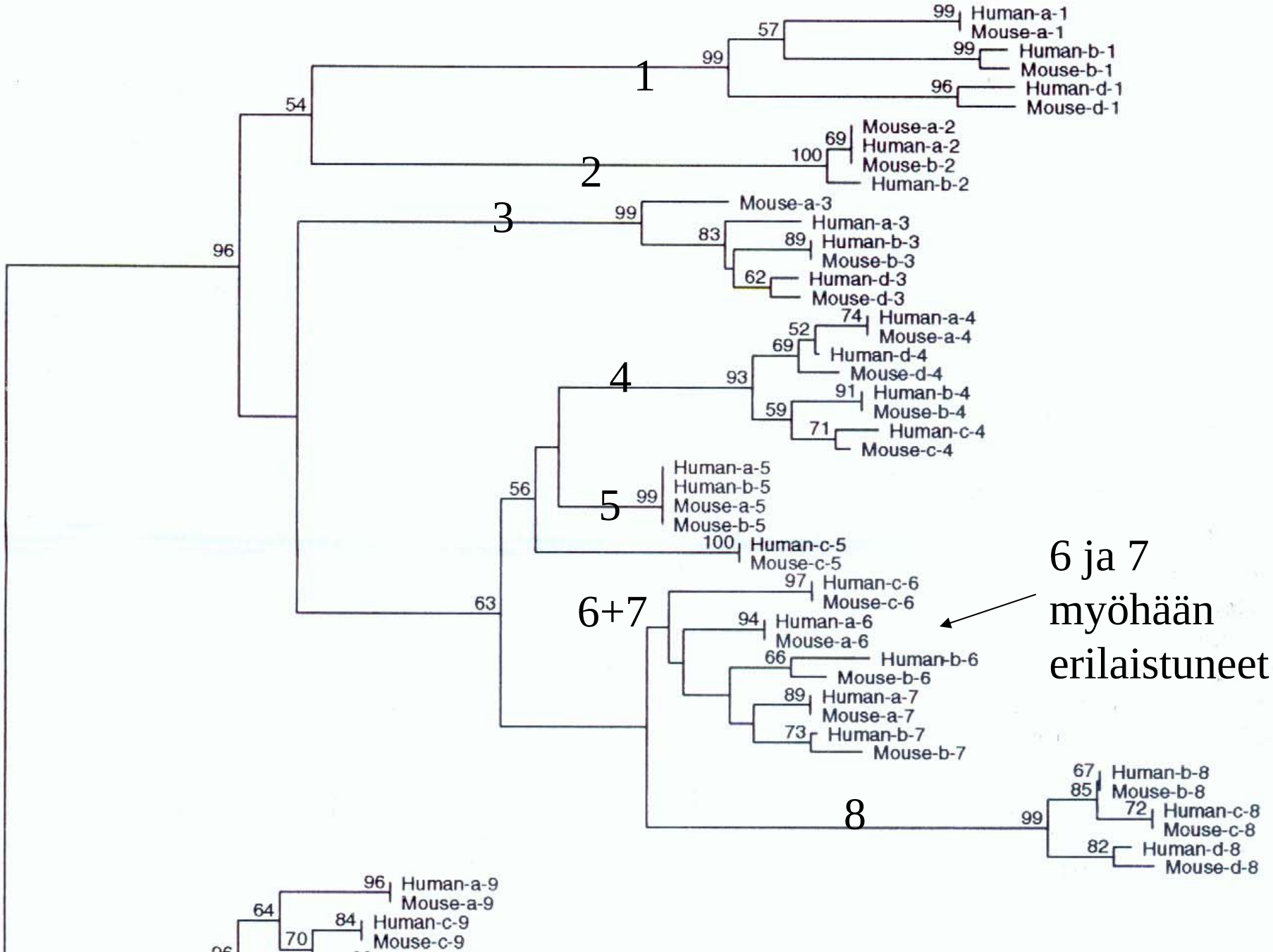
FIGURE 3.—Phylogenetic tree of 76 human and mouse *Antp*-class homeobox genes.

Ihmisen ja hiiren hox-geenien sukulaisuus

Geenit on nimetty kirjaimella a, b, c, d ja numerolla 1, 2, 3 …

Samanumeroiset ovat läheistä sukua toisilleen, kirjaimesta riippumatta

Se osoittaa, että numerolla merkityt sarjat kehittyivät erilaisiksi ensin, ja sitten tapahtui sarjojen monistuminen


Human-a-1
Mouse-a-1
Human-b-1
Mouse-b-1
Human-d-1
Mouse-d-1
1
Mouse-a-2
Human-a-2
Mouse-b-2
Human-b-2
2
Mouse-a-3
Human-a-3
Human-b-3
Mouse-b-3
Human-d-3
Mouse-d-3
3
Human-a-4
Mouse-a-4
Human-d-4
Mouse-d-4
Human-b-4
Mouse-b-4
Human-c-4
Mouse-c-4
4
Human-a-5
Human-b-5
Mouse-a-5
Mouse-b-5
5
Human-c-5
Mouse-c-5
Human-c-6
Mouse-c-6
Human-a-6
Mouse-a-6
Human-b-6
Mouse-b-6
Human-a-7
Mouse-a-7
Human-b-7
Mouse-b-7
6+7
6 ja 7 myöhään erilaistuneet
Human-b-8
Mouse-b-8
Human-c-8
Mouse-c-8
Human-d-8
Mouse-d-8
8
Human-a-9
Mouse-a-9
Human-c-9
Mouse-c-9

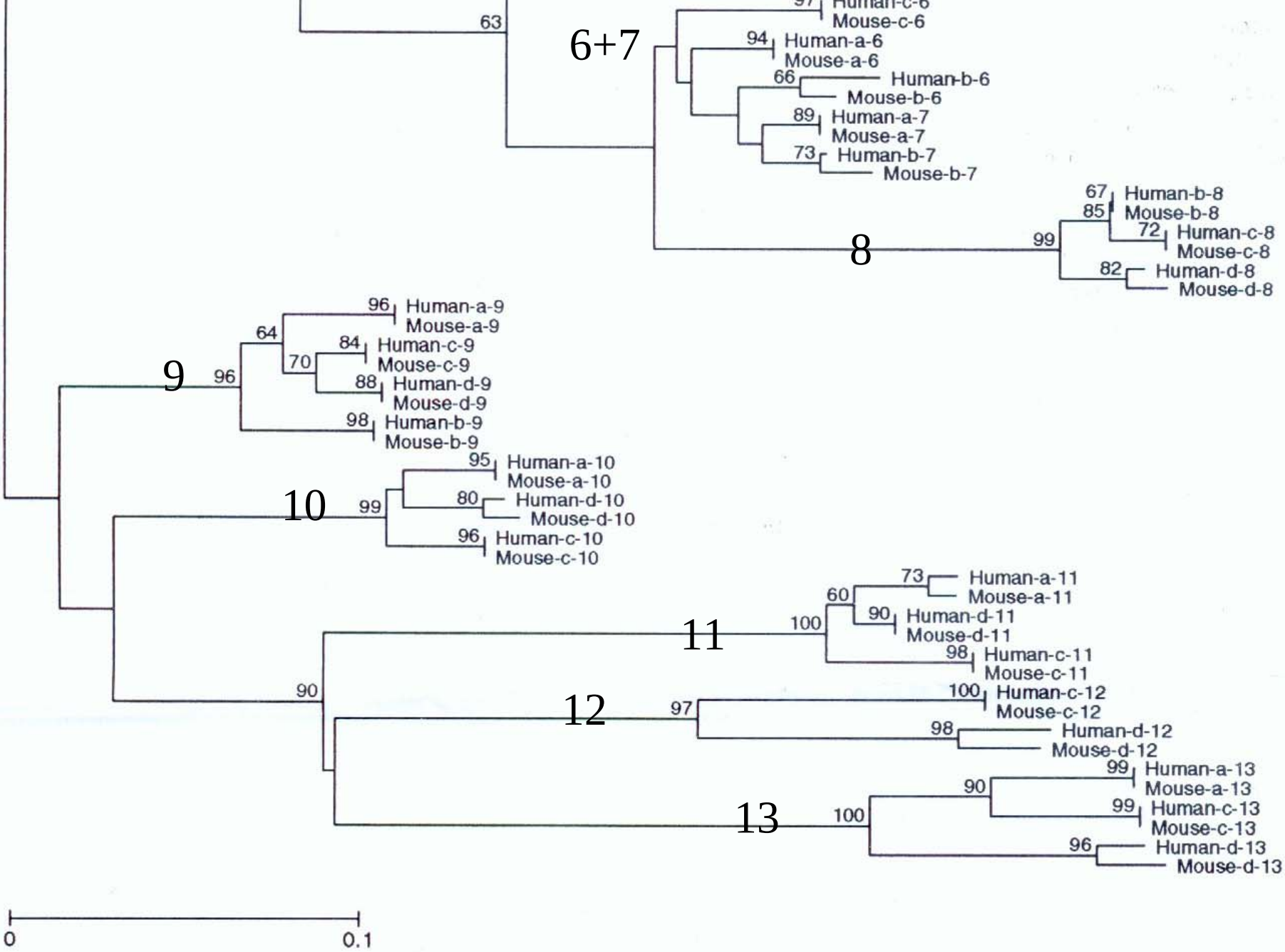
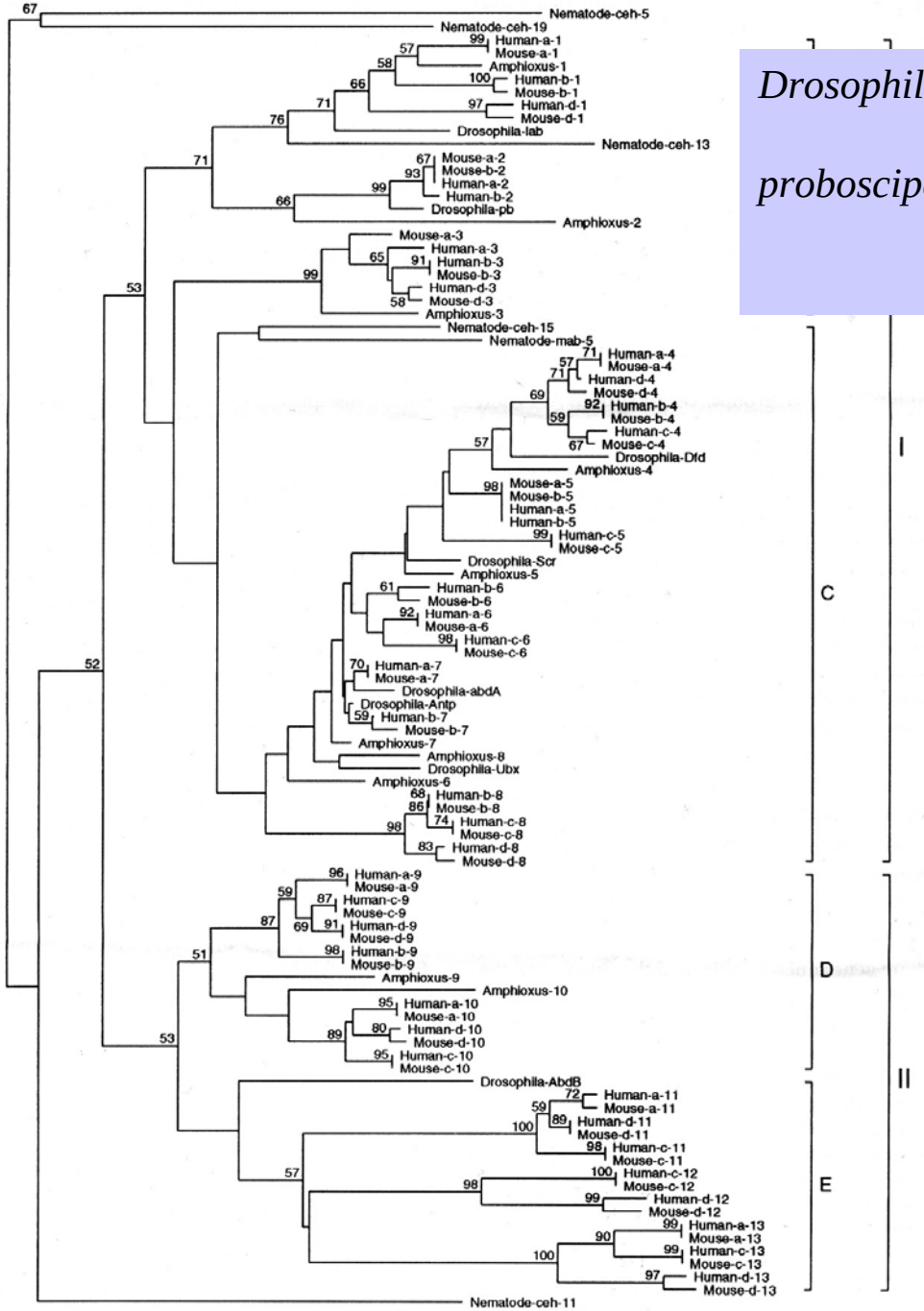
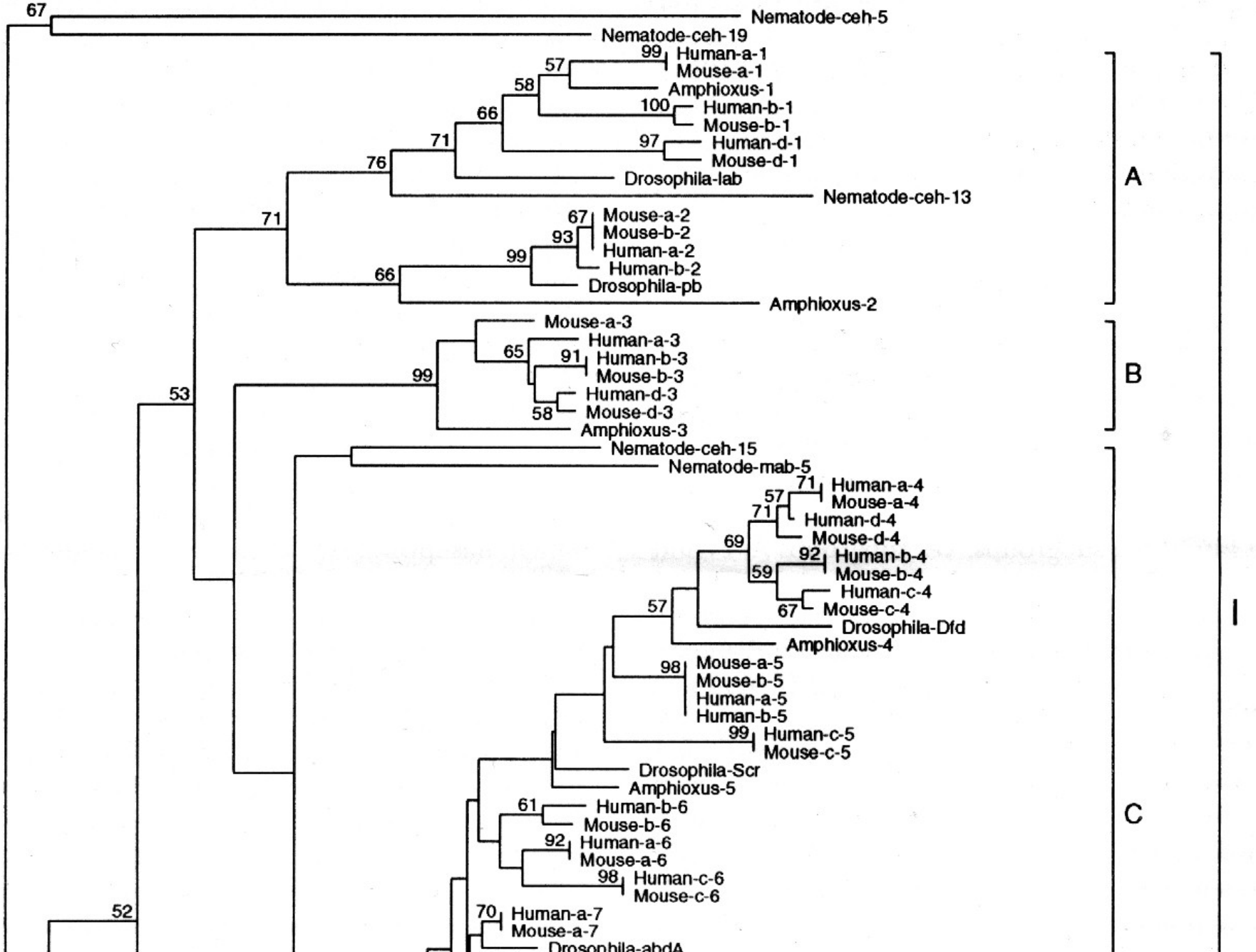


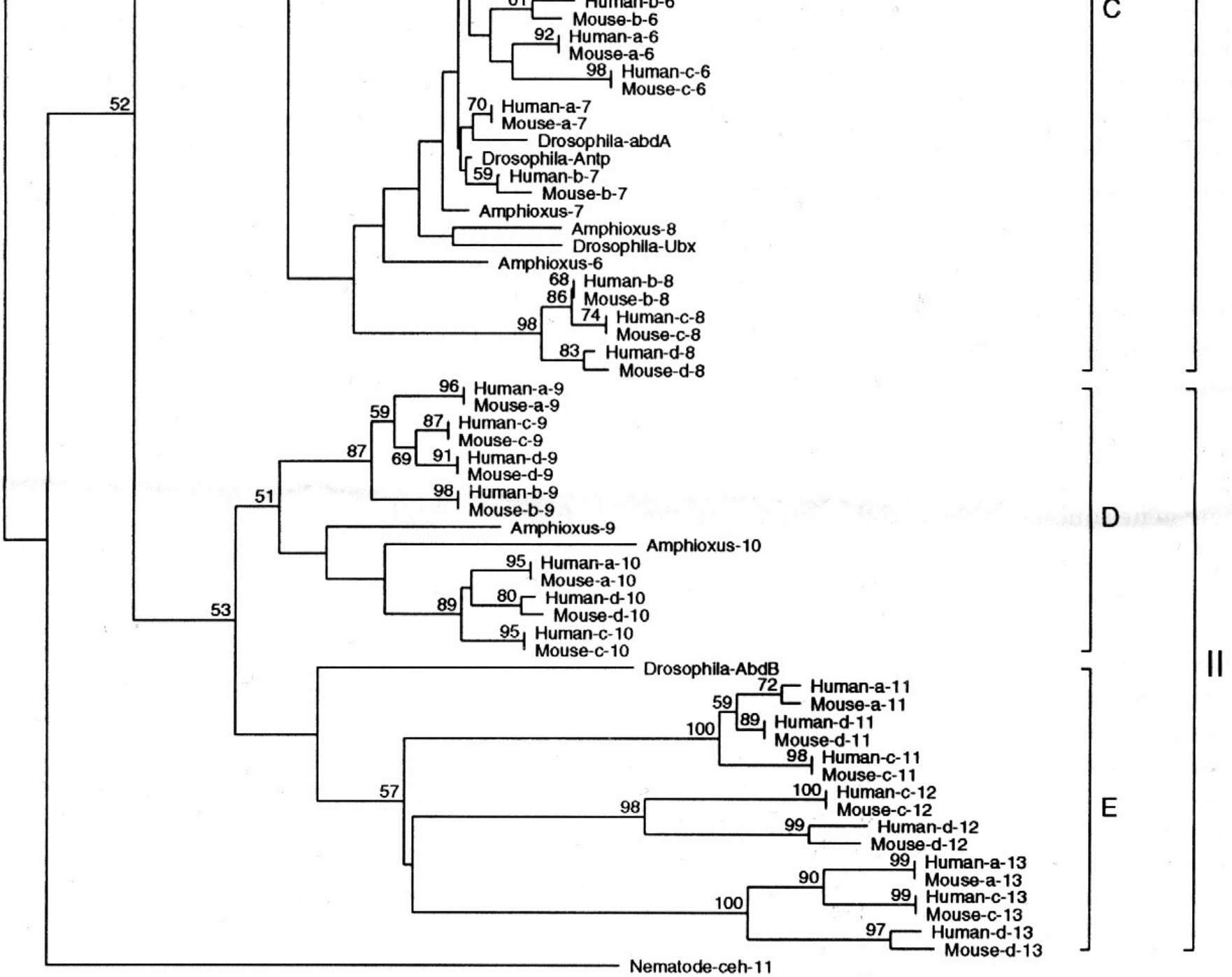
FIGURE 3.—Phylogenetic tree of 76 human and mouse *Antp*-class homeobox genes.



*Drosophila*n *labial* ja nisäkkään ykkönen

proboscipedia ja nisäkkään kakkonen


67
Nematode-ceh-5
Nematode-ceh-19
99
Human-a-1
Mouse-a-1
57
58
Amphioxus-1
100
Human-b-1
Mouse-b-1
66
71
97
Human-d-1
Mouse-d-1
76
Drosophila-lab
Nematode-ceh-13
A
71
67
Mouse-a-2
Mouse-b-2
93
Human-a-2
99
Human-b-2
66
Drosophila-pb
Amphioxus-2
Mouse-a-3
Human-a-3
65
91
Human-b-3
Mouse-b-3
99
53
Human-d-3
58
Mouse-d-3
Amphioxus-3
B
Nematode-ceh-15
Nematode-mab-5
71
Human-a-4
57
Mouse-a-4
71
Human-d-4
Mouse-d-4
69
92
Human-b-4
59
Mouse-b-4
Human-c-4
67
Mouse-c-4
57
Drosophila-Dfd
Amphioxus-4
98
Mouse-a-5
Mouse-b-5
Human-a-5
Human-b-5
99
Human-c-5
Mouse-c-5
Drosophila-Scr
Amphioxus-5
61
Human-b-6
Mouse-b-6
92
Human-a-6
Mouse-a-6
98
Human-c-6
Mouse-c-6
C
52
70
Human-a-7
Mouse-a-7
Drosophila-abdA
I


Human-b-6
Mouse-b-6
92
Human-a-6
Mouse-a-6
98
Human-c-6
Mouse-c-6
52
70
Human-a-7
Mouse-a-7
Drosophila-abdA
Drosophila-Antp
59
Human-b-7
Mouse-b-7
Amphioxus-7
Amphioxus-8
Drosophila-Ubx
Amphioxus-6
68
Human-b-8
86
Mouse-b-8
74
Human-c-8
98
Mouse-c-8
83
Human-d-8
Mouse-d-8
C
96
Human-a-9
Mouse-a-9
59
87
Human-c-9
Mouse-c-9
87
69
91
Human-d-9
Mouse-d-9
98
Human-b-9
51
Mouse-b-9
Amphioxus-9
Amphioxus-10
95
Human-a-10
Mouse-a-10
80
Human-d-10
89
Mouse-d-10
53
95
Human-c-10
Mouse-c-10
D
Drosophila-AbdB
72
Human-a-11
59
Mouse-a-11
89
Human-d-11
100
Mouse-d-11
98
Human-c-11
Mouse-c-11
57
100
Human-c-12
98
Mouse-c-12
99
Human-d-12
Mouse-d-12
99
Human-a-13
90
Mouse-a-13
99
Human-c-13
100
Mouse-c-13
97
Human-d-13
Mouse-d-13
E
II
Nematode-ceh-11

Homeoottisten selektorigeenien sarja on monisoluisten eliöiden yhteistä perintöä

Selkärankaisten syntyessä (suikulaisen kaltaisesta, *Amphioxus*) koko sarja on tupla-tuplautunut, luultavasti koko genomin tupla-tuplautuessa

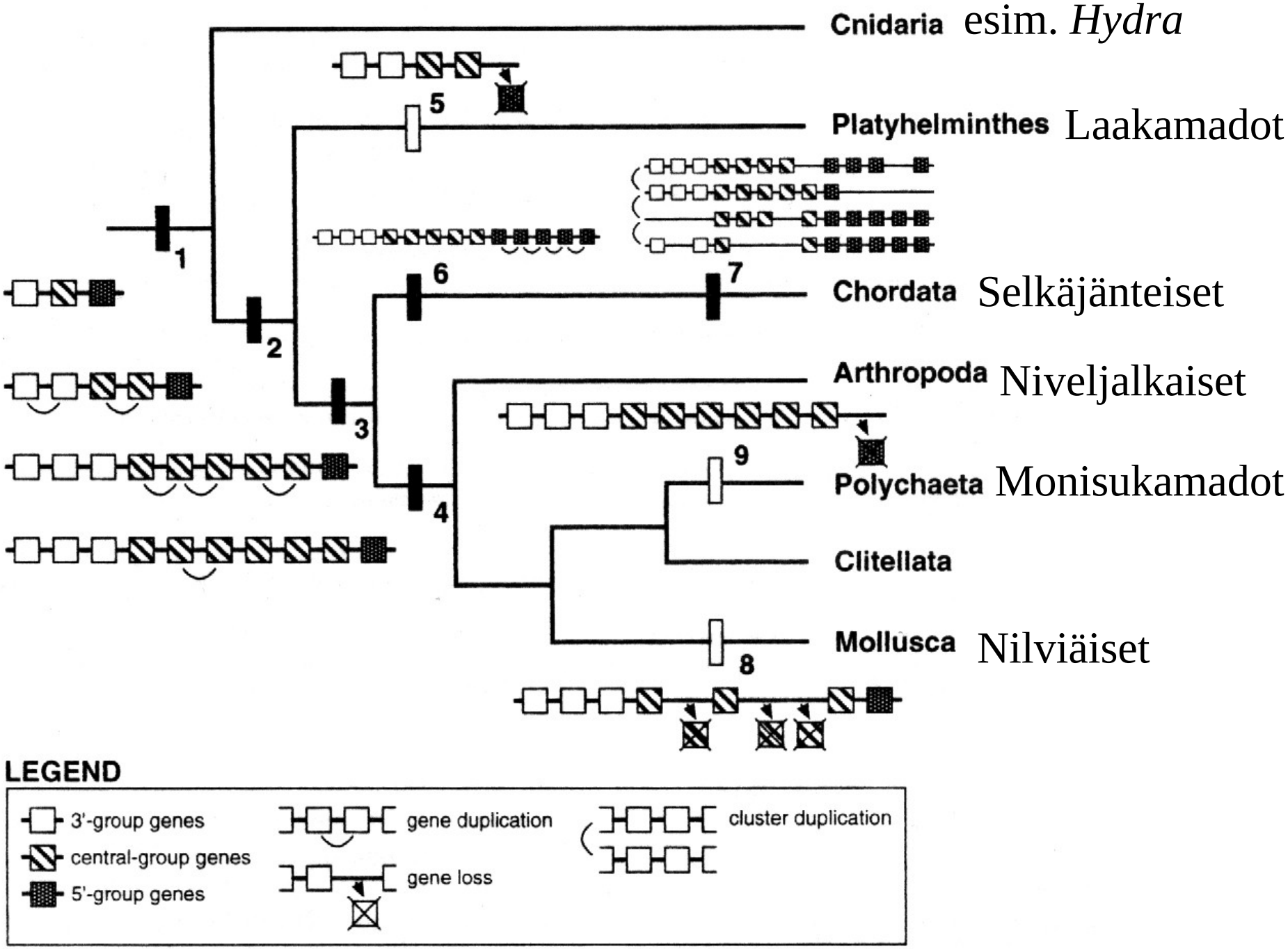
diploidi > tetraploidi > oktoploidi

Näistä polyploidisaatioista on runsaasti muitakin merkkejä selkärankaisten genomissa

Tuplautumisten jälkeen jotkut sarjan geeneistä ovat voineet rapautua tunnistamattomiksi, koska niitä ei ehkä tarvittu

Jäljelle jääneet, aluksi ylimääräiset geenit ovat hankkineet uusia tehtäviä, ja sen seurauksena selkärankaisten kehityksessä on ’voitu nostaa’ erilaistumisastetta

Huomatkaa, että duplikaatiot eivät ole darwinistisen evoluution tuotetta, vaan sattuman, mutta darwinistinen evoluutio on sitten voinut tarttua uuteen materiaaliin, mikäli sen muutokset ovat tuottaneet edullisia uudismuodostumia


Cnidaria
esim. *Hydra*
Platyhelminthes
Laakamadot
Chordata
Selkäjänteiset
Arthropoda
Niveljalkaiset
Polychaeta
Monisukamadot
Clitellata
Mollusca
Nilviäiset
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2
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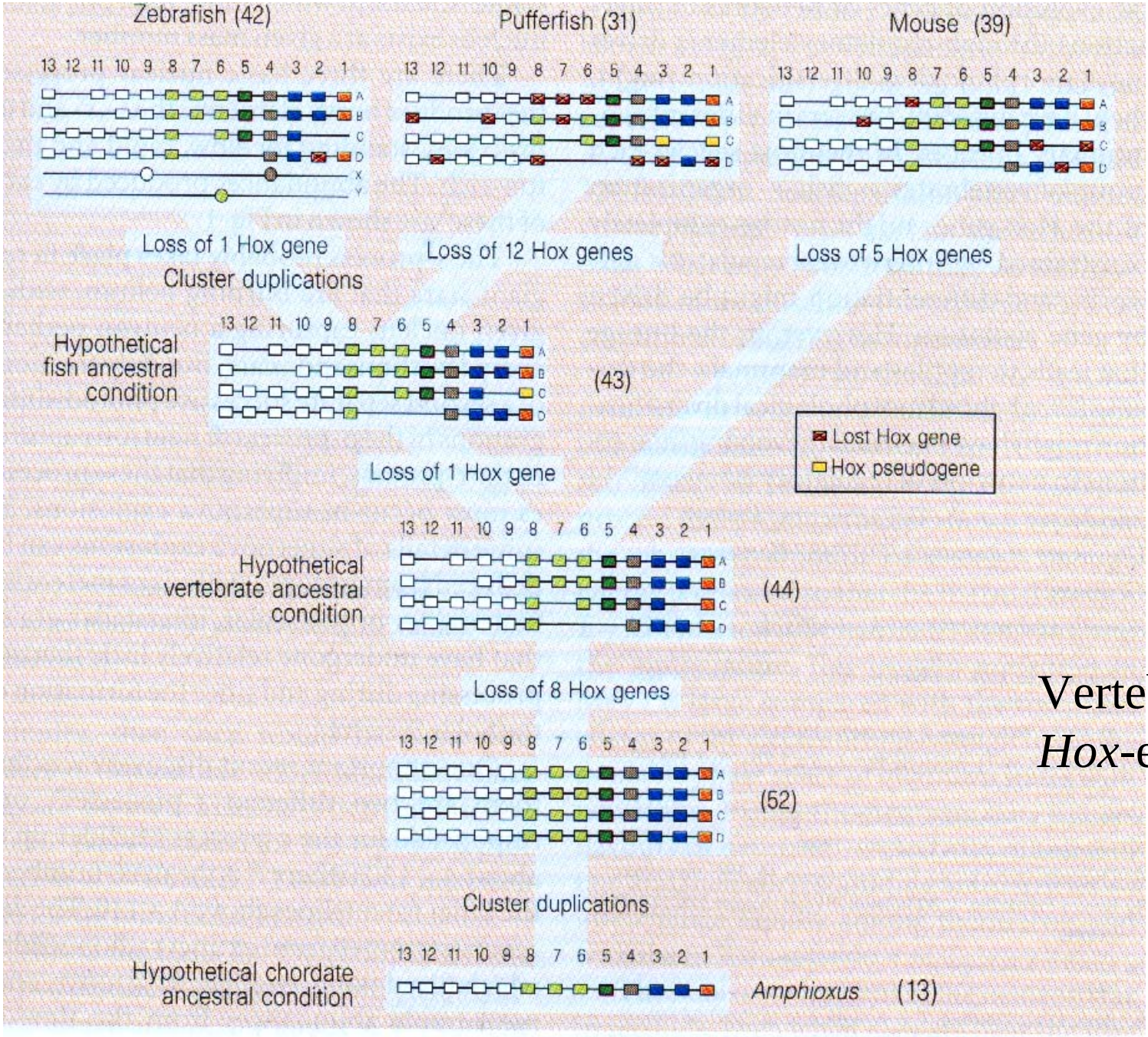
LEGEND
3'-group genes
central-group genes
5'-group genes
gene duplication
gene loss
cluster duplication



Vertebraattien
Hox-evoluutio

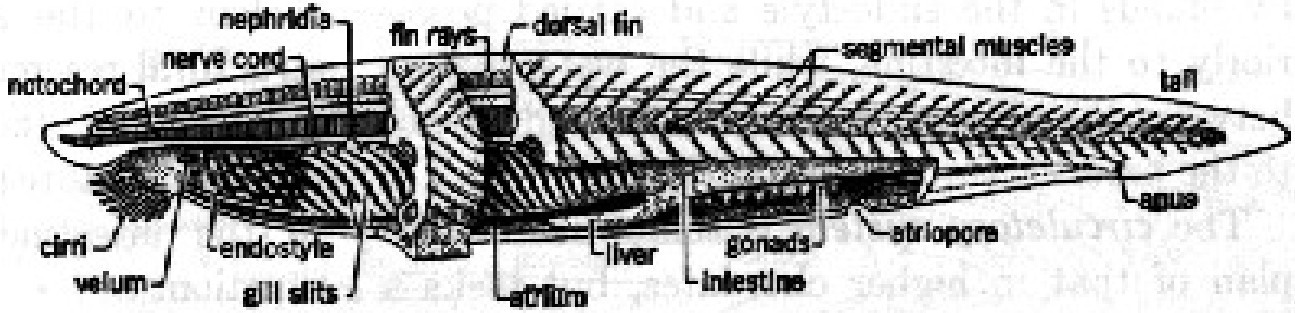


Fig. 28-11. Subphylum CEPHALOCHORDATA. The lancelet or amphioxus (*Branchiostoma*). Adult partly dissected from left side. Natural size about 2 inches long.

Suikulainen (*Branchiostoma*) eli amphioxus tai lancelet

ing: "if it could be demonstrated that any complex organ existed which could not possibly have been formed by numerous, successive, slight modifications, my theory would absolutely break down."

Näin kirjoitti Darwin. Meistä kaksi perättäistä genomin duplikaatiota ei ihan täytä "hienoisen modifikaation" määritelmää, mutta ne kuitenkin tuottivat vasta materiaalia, josta lisätyt pienet modifikaatiot ja luonnonvalinta yhdessä saivat aikaan melkoisia muutoksia.

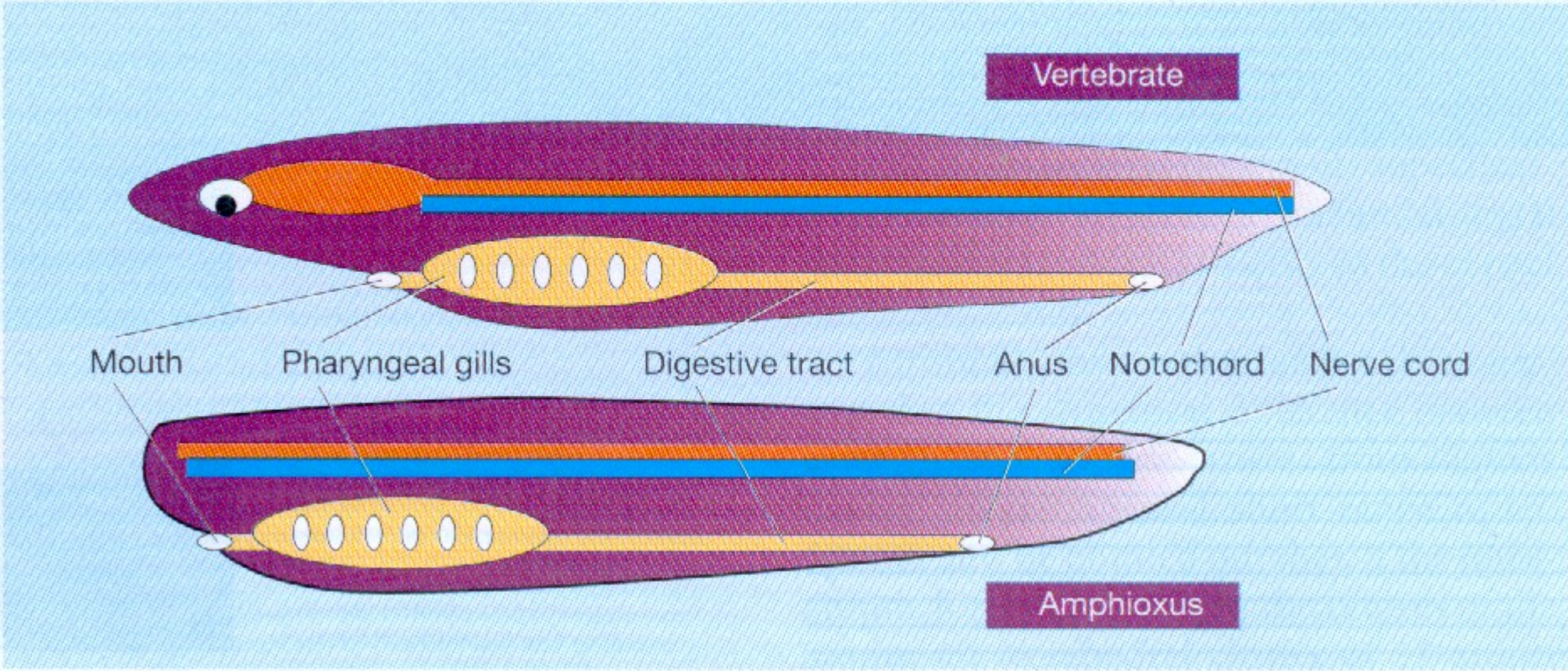


Figure 1 **The cephalochordate amphioxus compared to a primitive vertebrate (similar to a modern-day lamprey). The overall construction of the organisms is very similar, with a dorsal nerve cord, a more ventral axial skeleton known as the notochord, and a ventral digestive tract. Both creatures have gills in the pharyngeal region, structures that are designed to capture food or remove oxygen from the water. The notochord extends right to the front of amphioxus, but the vertebrate has a prominent head at the anterior end, extending beyond the notochord. Early in development, human embryos have a notochord that subsequently becomes greatly reduced, giving rise to the discs between the adult vertebrae.**

Nature15 Feb 2001

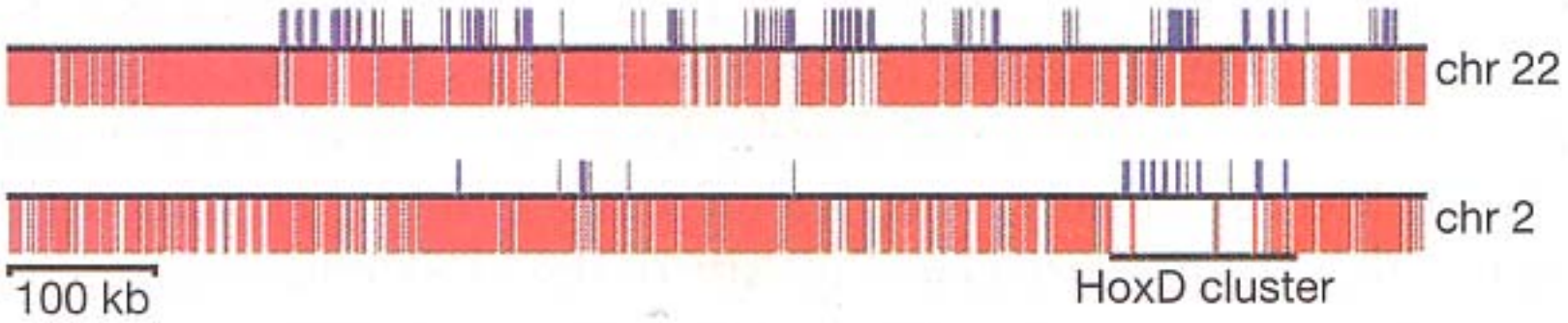


Figure 21 Two regions of about 1 Mb on chromosomes 2 and 22. Red bars, interspersed repeats; blue bars, exons of known genes. Note the deficit of repeats in the HoxD cluster, which contains a collection of genes with complex, interrelated regulation.

Ihmisen (nisäkkään) Hox-klusterien kohdalla ei genomiin ole päässyt iskostumaan joutavia toistojaksoja, koska homeoboksigeenien välitkin ovat säätelyn kannalta oleellisia. *Drosophilalla* niitä *Gypsy*, *412* ja *Doc* [Holliday] insertioita muutama oli, rauhallisissa labraoloissa. Luonnonvalintaa ne eivät kestäisi.

Antennapedia-bithorax -kompleksi (HOM) kaavamaisesti

jatk.

8 homeoottista selektorigeeniä

650 kb

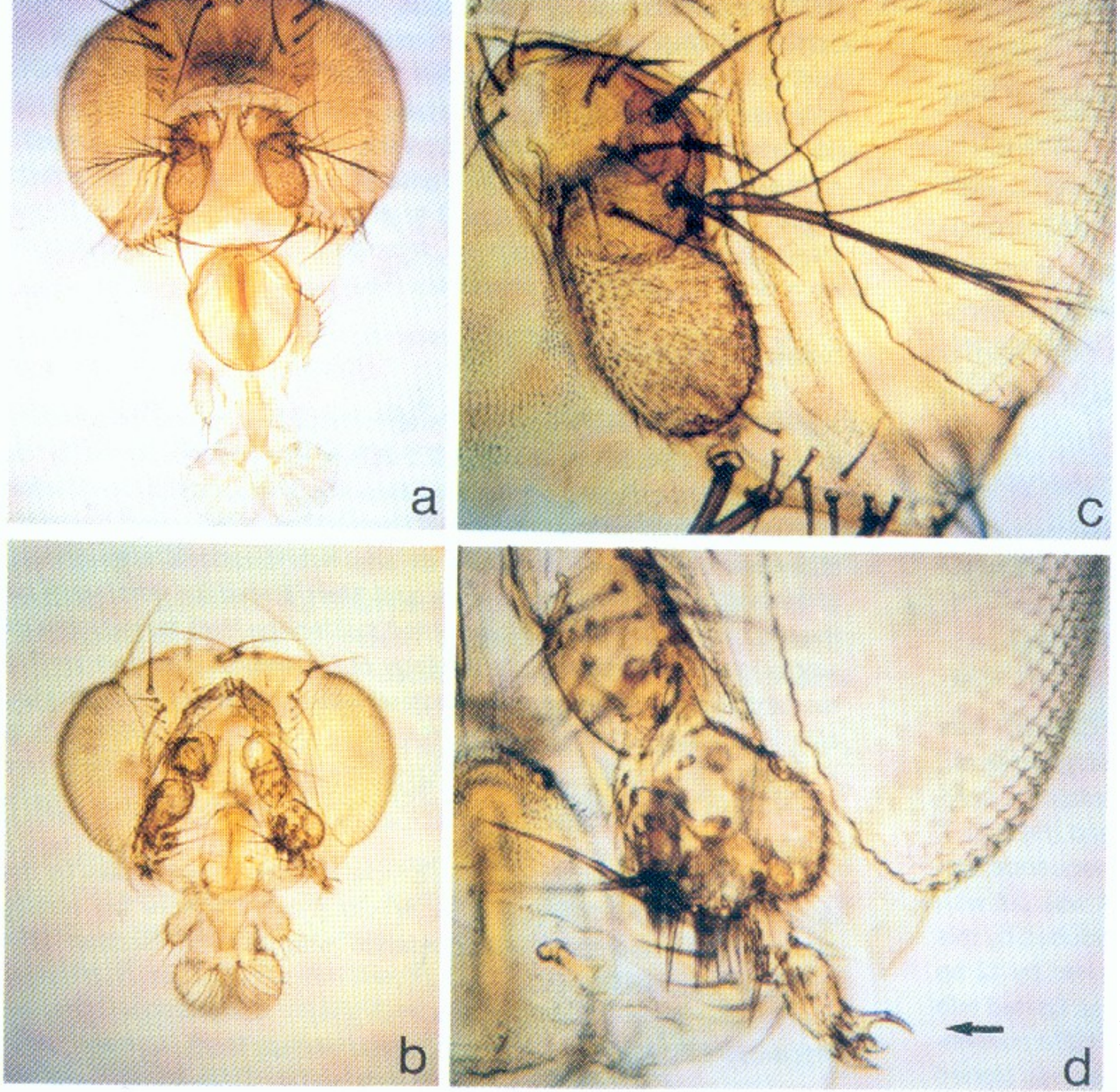
säätelyalueen sekvenssiaihe, joka “lukee” paikkatietoa

(paikkatietoa on *napaisuus-gap-segmentaatio- ja dorsoventral*-geenien proteiinit, niinkuin *eve*-esimerkissä: porkkana, sitruuna ja tomaatti)

selektorigeenin koodaava alue, jossa 60 aa homeoboksi

Eri eliöiden Hox-geenit ovat vieläkin niin samanlaisia, että ne voidaan saada toimimaan vieraassa ympäristössä

Seuraavassa kuvassa näkyy, miten hiiren *Hox2-2* *Drosophilaan* siirrettynä aiheuttaa jalan tuntosarven tilalle, vaikka se geeni on liipaistu käyntiinkin lämpöshokki-promoottorin avulla



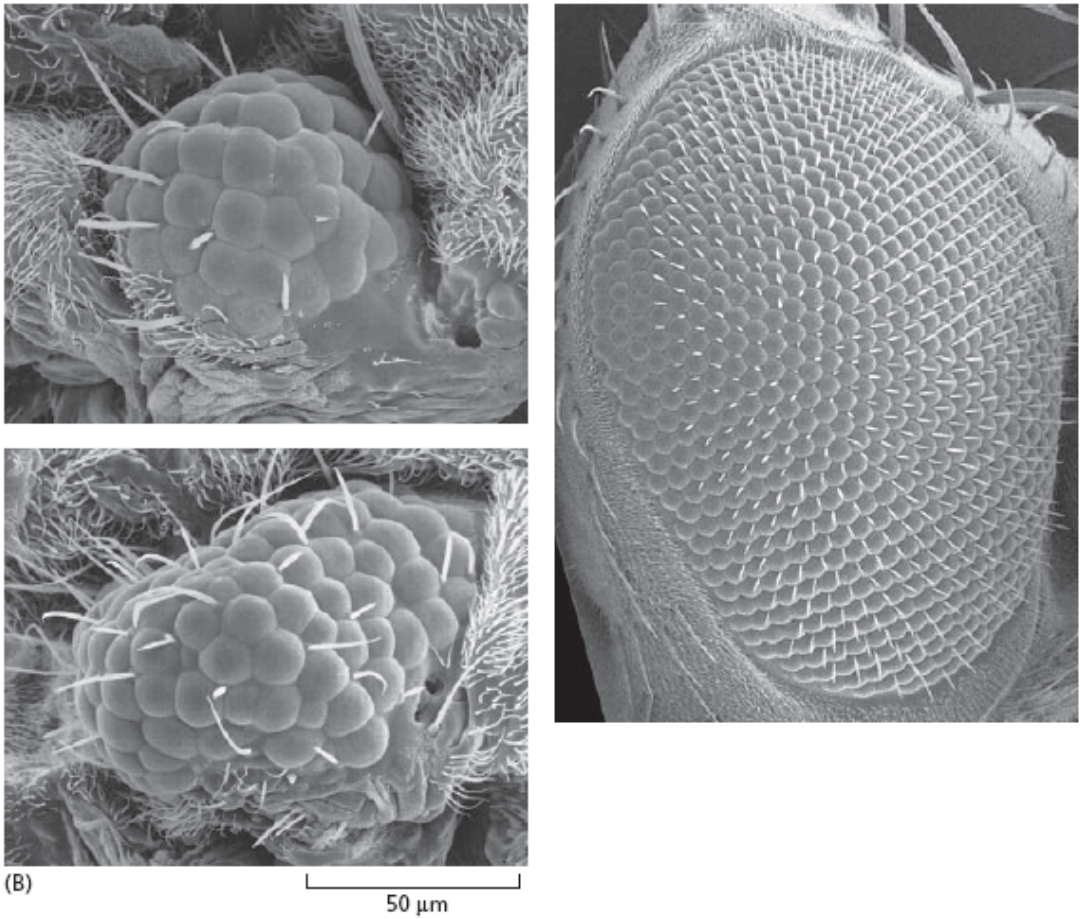
wt (wild type)

-kärpänen

hsp70-Hox-2.2

eli heat shock promoter ja hiiren Hox-geeni istutettuna *Drosophilaan*

Malicki *et al*. (1990) Cell 63: 961



Pax6 otettuna squidista eli mustekalasta istutettuna *Drosophilan* jalkaan aiheuttaa ektooppisen silmän

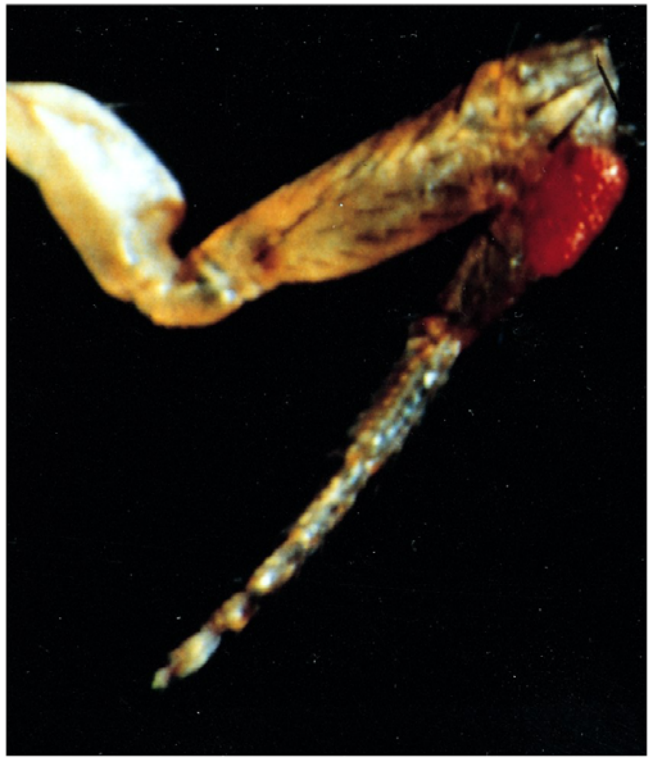


Figure 7-77b Molecular Biology of the Cell 5/e (© Garland Science 2008)

Eyeless ja *Pax6* ovat homologeja

CELL 466, 1306

Ihmisen (nisäkkään) hox-geenit

- sijaitsevat neljässä ryväksessä

- väliin ei ole voinut tunkea mitään roskaa

- mutaatiota vähän (koska mutaatiot tappavat)

- siis myös välit ovat tärkeitä: roska tappaa

- virheet ovat dominoivia ja tappavat jo heterotsygoottina

- ovatpa harvinaisen tylyjä geeneiksi!

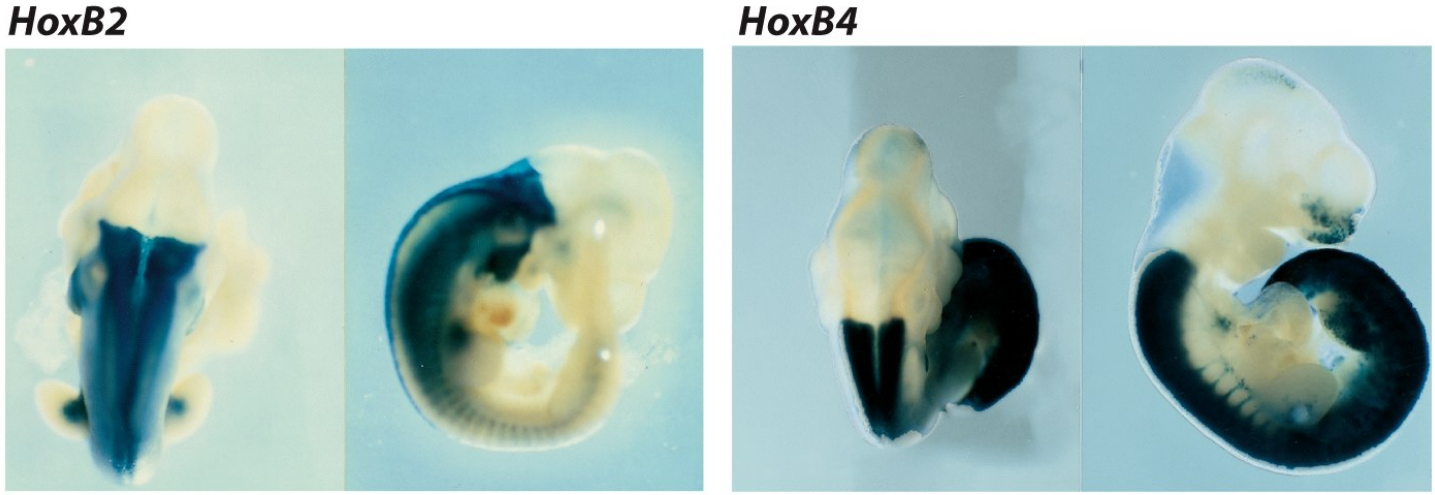
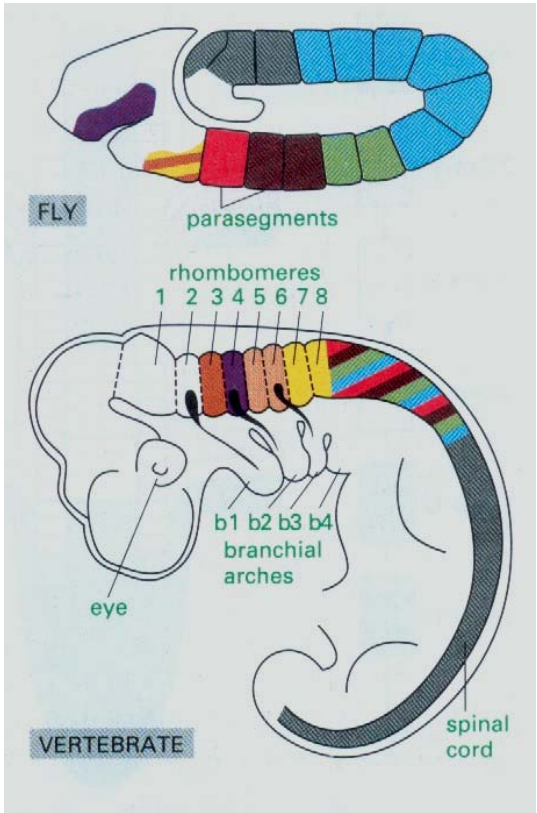
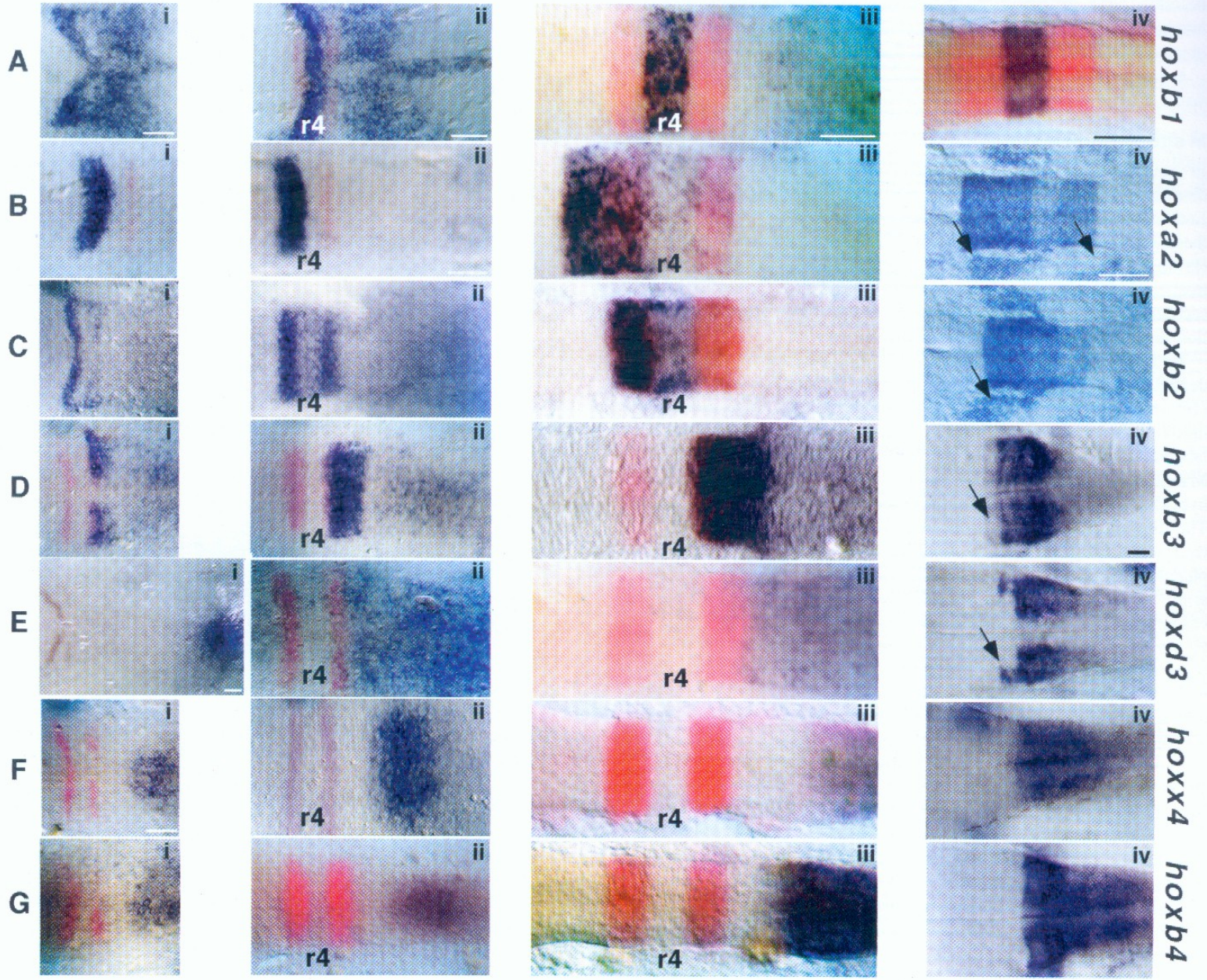


Figure 22-47 Molecular Biology of the Cell 5/e (© Garland Science 2008)



Hox-geenien ekspressio hiiren alkiossa ei voi olla ihan samanlaista kuin kärpäsellä, mutta samoja sääntöjä siinä on: antero-posteriorijärjestys ja geenien järjestys kromosomissa ovat samat (kautta koko eläinkunnan)



Seeprakalan *Hox*-geenien ekspressio kehittyvässä taka-aivossa

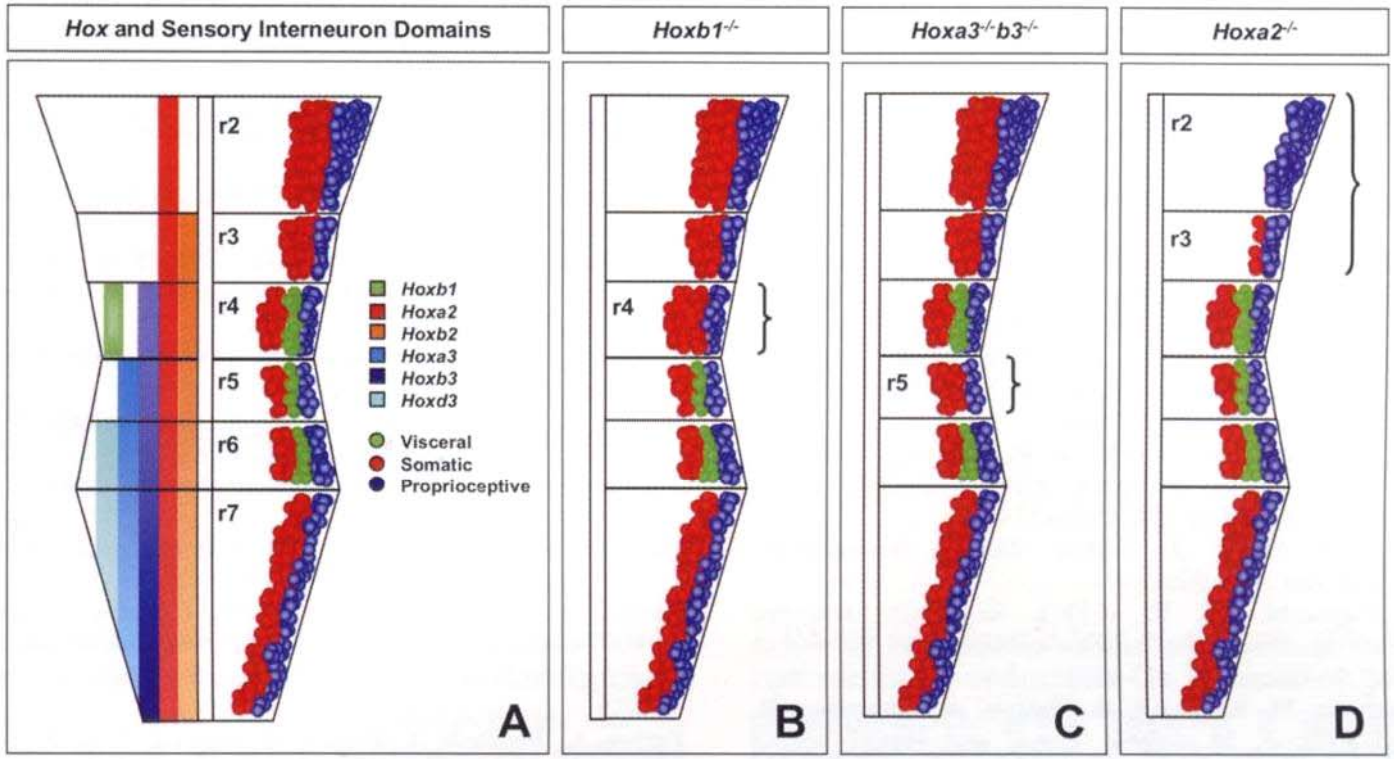
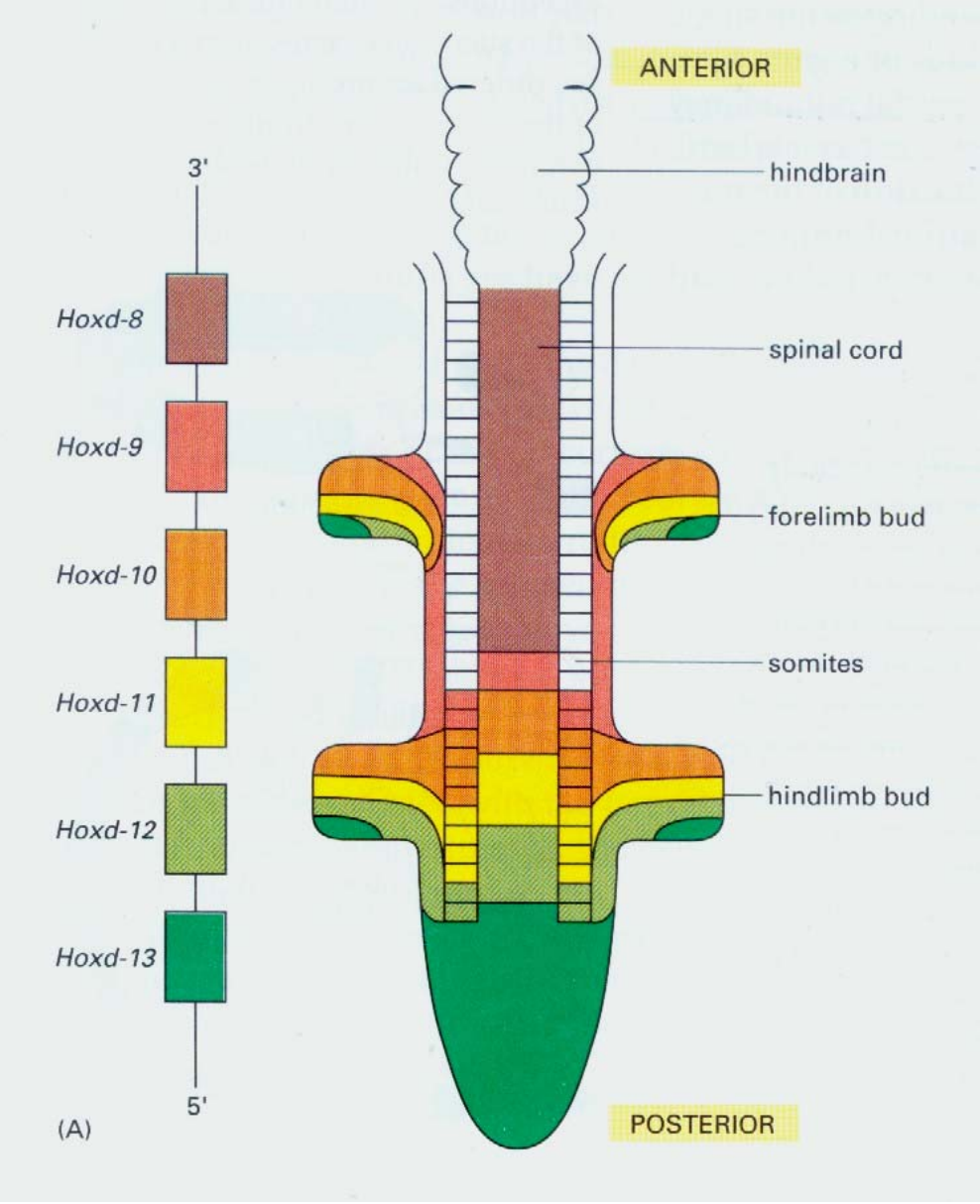
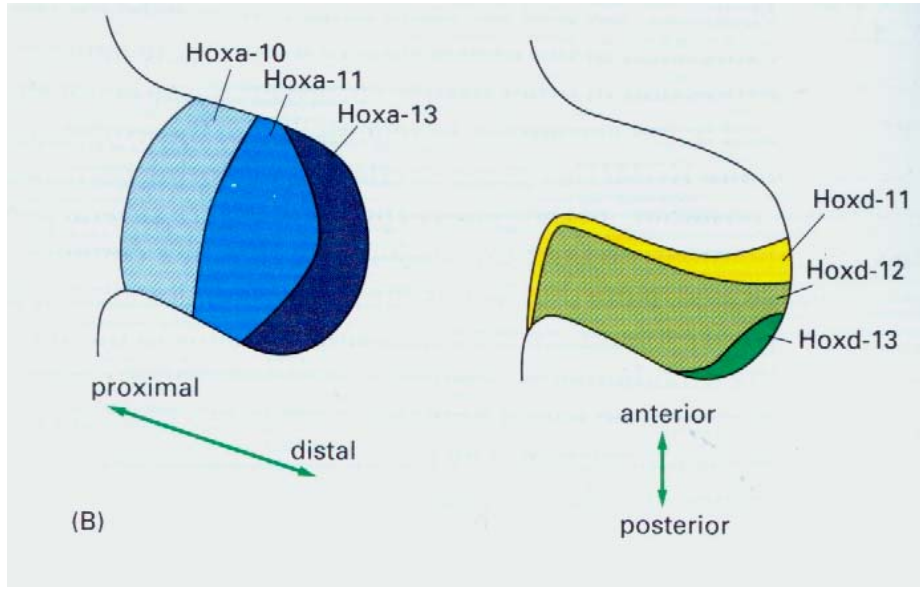


Fig. 7. Summary. (A) Schematic view of a flat-mount hindbrain showing Hox gene expression on the left (bars) and first-order visceral (noradrenergic), somatic and proprioceptive sensory relay interneurons (circles) on the right. The loss of *Hoxb1* (B) and the combination of *Hoxa3* and *Hoxb3* (C) result in a specific loss of visceral interneurons in r4 and r5, respectively. The loss of visceral sensory interneurons in these Hox mutant embryos is associated with the expansion of the somatic sensory interneuron domain. In *Hoxa2* loss-of-function (D), somatic sensory interneurons are completely eliminated in r2 and significantly reduced in r3, presumably through the redundant role of *Hoxb2* in this rhombomere (see A). Although Hox genes are expressed throughout the early neuroepithelium, the present finding suggests a specific role for Hox genes in the generation of cellular diversity in the developing hindbrain.

Hox-geenit määrittävät taka-aivossa syntyvien sensoristen välittäjäneuronien kohtalon. Mitä ne tekee, kuuluu fysiologian alaan, mutta luulen, että ne muuttaa aistimuksen ”tiedoksi”, joka on koodattu aivojen topologiaan. Kts Purkinjen solu **CELL 597**

Hoxa ja *Hoxd* -geenien rooli hiiren kehittyvässä raajassa





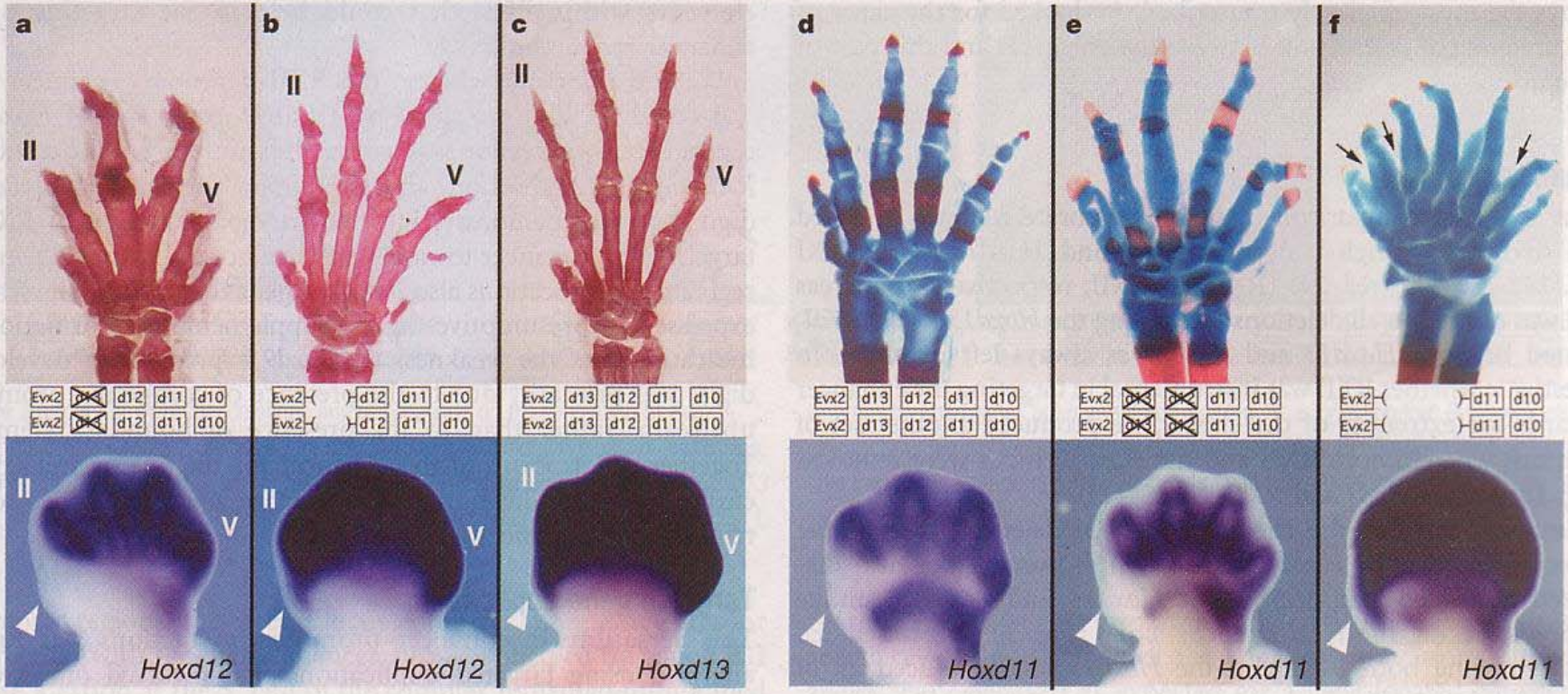


Figure 2 Targeted deletions induce regulatory reallocations. Comparison between digit phenotypes (top) and expression of 5′ *Hoxd* genes (bottom) associated with either the disruption or the deletion of the corresponding loci. Crosses indicate gene inactivation; brackets indicate deletion breakpoints. **a**, Inactivation of *Hoxd13* leads to an overall reduction in the size of digits, partial fusion between digits III and IV, and a supernumerary digit in most cases[23]. **b**, In contrast, deletion of the same locus has little effect (compare with control in **c**). In this latter case, a strong gain of expression of *Hoxd12* was scored, resembling the *Hoxd13* expression pattern (**b**, **c**). **f**, Deletion of both *Hoxd13* and *Hoxd12* loci induce a severe polydactyly, and fusions (arrows) indicate an even larger number of pre-chondrogenic condensations. **e**, This phenotype is not observed in the corresponding double inactivation allele. In this case, a robust gain of *Hoxd11* expression is associated with deletion of both *Hoxd13* and *Hoxd12* loci (**d**, **f**), whereas it is absent from the disruption of both loci (**e**). In both gains of expression (**b**, **f**), the profiles are reminiscent of wild-type *Hoxd13* (**c**), including in presumptive digit I (white arrowheads).

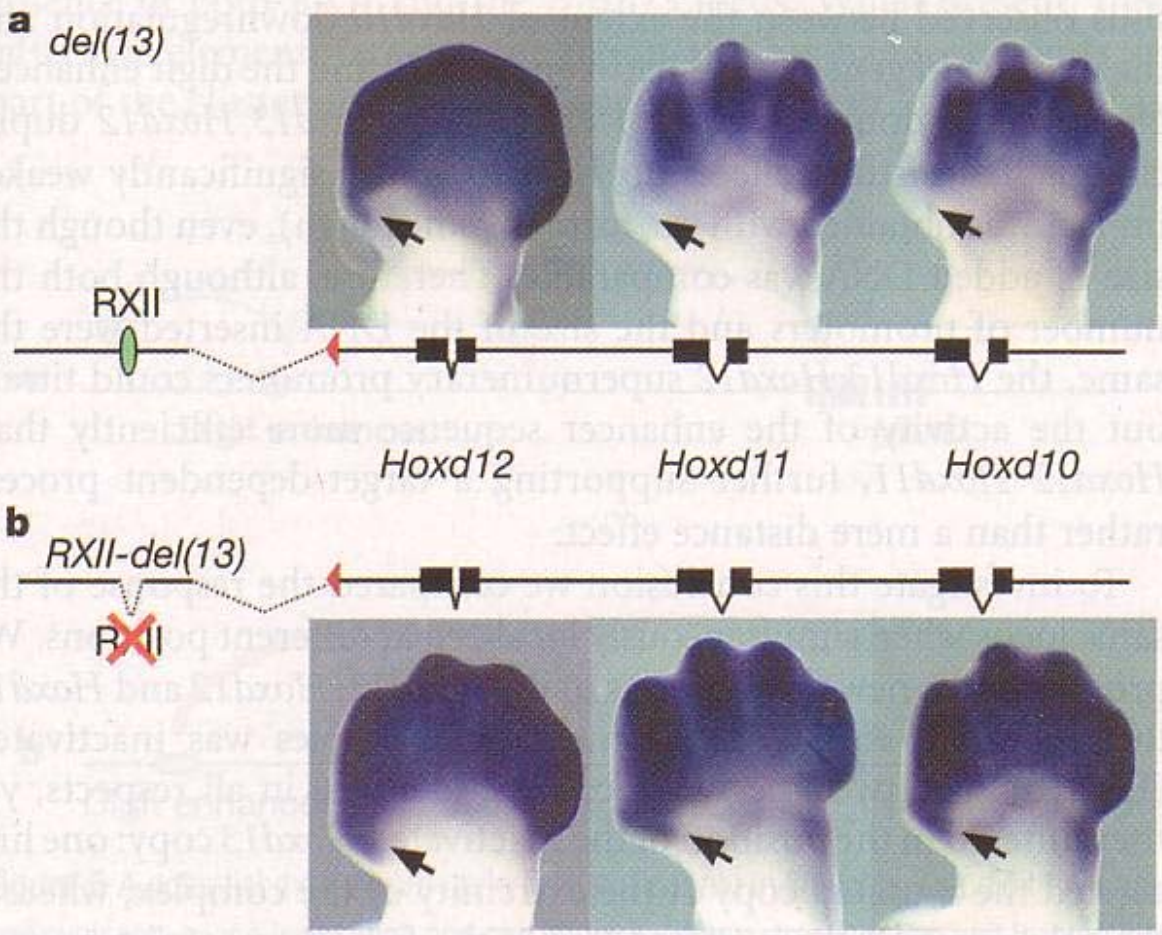


Figure 3 The evolutionarily conserved region RXII cooperates with the *Hoxd13* locus for positioning the enhancer in the 5′ end of the cluster. **a**, Expression of three neighbouring *Hoxd* genes in the limbs of 13.5-day-old embryos carrying a deletion of the *Hoxd13* locus. Although there is a gain of *Hoxd12* expression in the entire distal domain, both *Hoxd11* and *Hoxd10* transcription remains virtually unchanged. **b**, In contrast, further deletion of region XII, in the absence of the *Hoxd13* locus, induces a gain of expression for all three genes, including in presumptive digit I (black arrows), thus abrogating quantitative collinearity.

Nature 14 Nov 2002

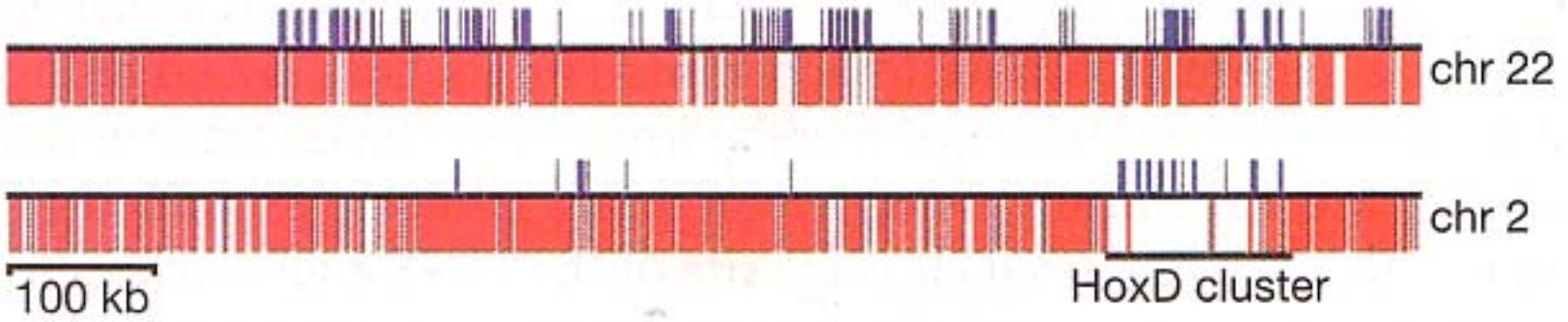


Figure 21 Two regions of about 1 Mb on chromosomes 2 and 22. Red bars, interspersed repeats; blue bars, exons of known genes. Note the deficit of repeats in the HoxD cluster, which contains a collection of genes with complex, interrelated regulation.

Nature15 Feb 2001

Ihmisen hox-geenien sijainnit

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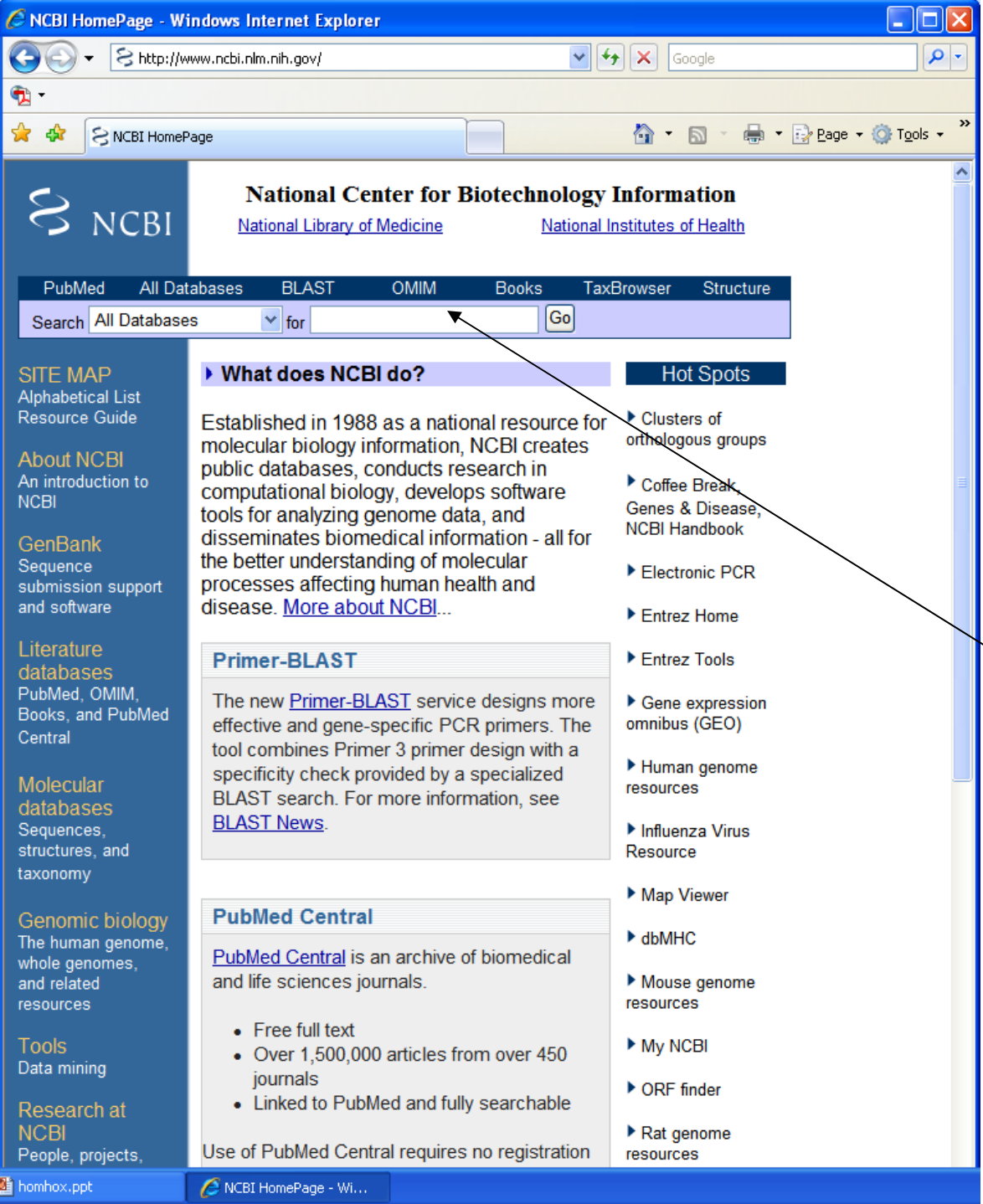
hoxb	17q21-q22
hoxc	12q13
hoxd	2q31-q32



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Welcome to OMIM®, Online Mendelian Inheritance in Man®. OMIM is a comprehensive, authoritative, and timely compendium of human genes and genetic phenotypes. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 12,000 genes. OMIM focuses on the relationship between phenotype and genotype. It is updated daily, and the entries contain copious links to other genetics resources.
This database was initiated in the early 1960s by Dr. Victor A. McKusick as a catalog of mendelian traits and disorders, entitled Mendelian Inheritance in Man (MIM). Twelve book editions of MIM were published between 1966 and 1998. The online version, OMIM, was created in 1985 by a collaboration between the National Library of Medicine and the William H. Welch Medical Library at Johns Hopkins. It was made generally available on the internet starting in 1987. In 1995, OMIM was developed for the World Wide Web by NCBI, the National Center for Biotechnology Information.
OMIM is authored and edited at the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, under the direction of Dr. Ada Hamosh.
NOTE: OMIM is intended for use primarily by physicians and other professionals concerned with genetic disorders, by genetics researchers, and by advanced students in science and medicine. While the OMIM database is open to the public, users seeking information about a personal medical or genetic condition are urged to consult with a qualified physician for diagnosis and for answers to personal questions.
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History
Clipboard
Details
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Titles
Show
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Send to
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OMIM UniSTS: 42
OMIM dbSNP: 25
Items 1 - 20 of 282
Page
1
of 15
Next
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LEUKEMIA, ACUTE LYMPHOBLASTIC, SUSCEPTIBILITY TO, INCLUDED
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Homeotic selector genes (3)
homhox.ppt
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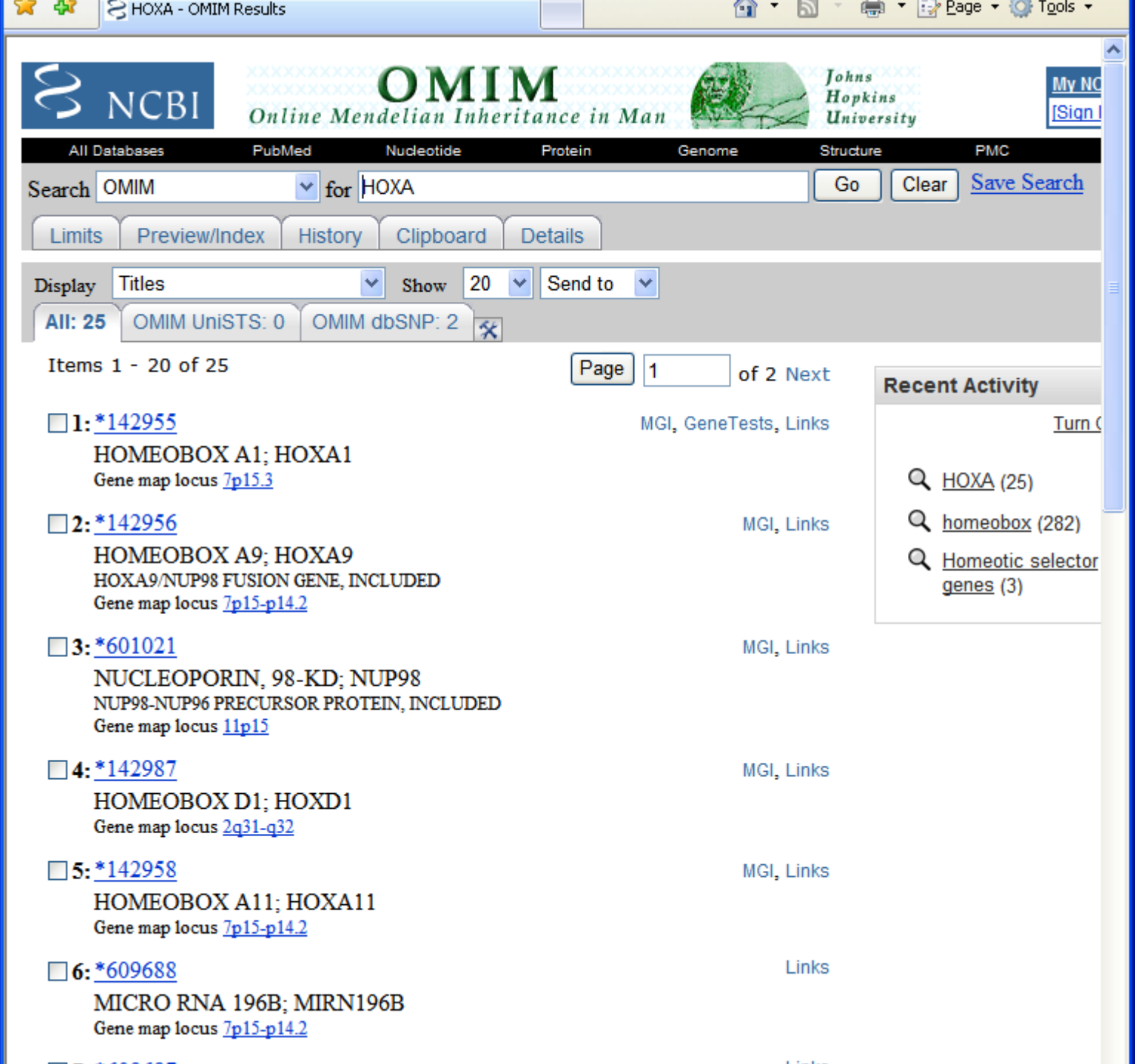
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Clipboard
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Items 1 - 20 of 25
Page
1
of 2
Next
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HOMEOBOX A1; HOXA1
Gene map locus 7p15.3
2: *142956
MGI, Links
HOMEOBOX A9; HOXA9
HOXA9/NUP98 FUSION GENE, INCLUDED
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Gene map locus 7p15-p14.2
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MICRO RNA 196B; MIRN196B
Gene map locus 7p15-p14.2
Recent Activity
Turn
HOXA (25)
homeobox (282)
Homeotic selector genes (3)

The OMIM Gene map presents the cytogenetic map location of disease genes and other expressed genes described in OMIM. See the OMIM Morbid Ma disease genes organized by disease. For more refined maps of genes and DNA segments click on the **Location** to invoke NCBI Entrez Map Viewer.

Search for: Find Find Next (from the current location)

- Enter gene symbol, chromosomal location, or disorder keyword to search for, e.g. "CYP1", "5", "1pter", "Xq", or "alzheimer".
- You must capitalize X and Y to search for those chromosomes.

7p15.3, HOXA1 to 7p15-p14, GGCT

<<Move Up

Location	Symbol	Title	MIM #	Disorder	Comments	Me
7p15.3	HOXA1, HOX1F, BSAS	Homeo box-A1	142955	Bosley-Salih-Alorainy syndrome, 601536 (3); Athabaskan brainstemdysgenesis syndrome, 601536 (3)		RE, Fd
7p15.3	KLHL7	Kelch-like 7	611119			REc
7p15.3-p15.2	INMT	Indolethylamine N-methyltransferase	604854			REa
7p15.2	CYCS, CYC, THC4	Cytochrome C, somatic	123970	Thrombocytopenia 4, 612004 (3)		REc
7p15.2-p15.1	PSP	Phosphoserine phosphatase	172480	Phosphoserine phosphatase deficiency (3)		S, D
7p15.1	NPY	Neuropeptide Y	162640			REa A
7p15.1	WIPF3, CR16	WAS/WASL-interacting protein family, member 3	612432			REc
7p15.1	ZNRF2	Zinc finger and ring finger protein 2	612061			REc
7p15	AHR	Aryl hydrocarbon receptor	600253			REa Psh
7p15	CDCA7L, R1, JPO2	Cell division cycle-associated protein 7-like	609685			REc

MIM *142955
Cloning
Mapping
Molecular Genetics
Animal Model
Allelic Variants
View List
References
Contributors
Creation Date
Edit History

Gene map

Entrez Gene
Nomenclature
RefSeq
GenBank
Protein
UniGene

LinkOut
HGMD
GAD
MGI

*142955
HOMEOBOX A1; HOXA1

GeneTests, Links

Alternative titles; symbols

HOMEOBOX 1F; HOX1F
Hox-1.6, MOUSE, HOMOLOG OF
lab, DROSOPHILA, HOMOLOG OF

Gene map locus 7p15.3

TEXT

CLONING

See 142950. In vertebrates, the genes encoding the class of transcription factors called homeobox genes are found in clusters named A, B, C, and D on 4 separate chromosomes. Expression of these proteins is spatially and temporally regulated during embryonic development. Hong et al. (1995) determined the structure of the first gene in the homeobox A cluster, HOXA1, by cloning its full-length cDNA, which predicts a protein of 335 amino acids. In vitro translation produced the expected 36-kD protein. An alternatively spliced cDNA was also obtained. In PA-1 teratocarcinoma cells, HOXA1 was induced by retinoic acid earlier than other HOXA cluster genes.

MAPPING

Apiou et al. (1996) used fluorescence in situ hybridization to localize the HOXA gene cluster precisely to 7p15.3.

MOLECULAR GENETICS

Autism Spectrum Disorder Susceptibility

Ingram et al. (2000) identified a common polymorphism in the HOXA1 gene: an A-to-G substitution at codon 218, changing the codon for one histidine in a series of histidine repeats to an arginine at position 73. The frequency of the G allele was 20 to 60% among the Coriell Human Diversity Panel, but was not identified in any individuals of Asian origin including Indians, Japanese, and Chinese. The frequency of the G allele was 0.202 in 57 probands with autism spectrum disorders and 0.203 in their 32 affected relatives. The frequency of the G allele in 134 unaffected relatives of subjects with an Asperger spectrum disorder was 0.164. The frequency of the G allele in the convenience population for this study was 0.109. In the autism spectrum disorder families, there was a significant deviation from the HOXA1 genotype ratios expected from Hardy-Weinberg proportions. Among affected offspring, a significant deviation from mendelian expectation in gene transmission was observed. Ingram et al. (2000) suggested that there was evidence of an interaction between HOXA1, HOXB1, and gender in susceptibility to autism spectrum disorders.

*142955 GeneTests, Links HOMEOBOX A1; HOXA1

Autism Spectrum Disorder Susceptibility

Ingram et al. (2000) identified a common polymorphism in the HOXA1 gene: an A-to-G substitution at codon 218, changing the codon for one histidine in a series of histidine repeats to an arginine at position 73. The frequency of the G allele was 20 to 60% among the Coriell Human Diversity Panel, but was not identified in any individuals of Asian origin including Indians, Japanese, and Chinese. The frequency of the G allele was 0.202 in 57 probands with autism spectrum disorders and 0.203 in their 32 affected relatives. The frequency of the G allele in 134 unaffected relatives of subjects with an Asperger spectrum disorder was 0.164. The frequency of the G allele in the convenience population for this study was 0.109. In the autism spectrum disorder families, there was a significant deviation from the HOXA1 genotype ratios expected from Hardy-Weinberg proportions. Among affected offspring, a significant deviation from mendelian expectation in gene transmission was observed. Ingram et al. (2000) suggested that there was evidence of an interaction between HOXA1, HOXB1, and gender in susceptibility to autism spectrum disorders.

*142955 GeneTests, Links HOMEOBOX A1; HOXA1

Bosley-Salih-Alorainy/Athabaskan Brainstem Dysgenesis Syndromes

Tischfield et al. (2005) carried out SNP-based linkage analysis in a Saudi Arabian family with Bosley-Salih-Alorainy syndrome (BSAS; 601536) and identified a single, fully informative 8.5-Mb region on 7p15.3-p14.3 in which only the affected children were homozygous. Further analysis narrowed the linkage to a region of homozygosity of approximately 300 kb on 7p15.2. Because of similarities between the BSAS phenotype and the pathology of the Hoxa1 -/- mouse, and because the HOXA cluster falls in the haploidentical region, Tischfield et al. (2005) analyzed the HOXA1 gene in Saudi Arabian individuals with BSAS and found a homozygous guanine insertion, 175-176insG, predicted to result in a reading frameshift and the introduction of a premature stop codon (142955.0001). A Turkish individual with BSAS had a homozygous 84C-G transversion resulting in the substitution of a stop codon for a tyrosine residue (Y28X; 142955.0002). Noting the phenotypic overlap of BSAS, the Hoxa1 knockout mouse, and Athabaskan brainstem dysgenesis syndrome, Tischfield et al. (2005) analyzed genomic DNA from 5 of the reported individuals with ABDS and 4 of their phenotypically normal parents. All 5 affected individuals were homozygous across the HOXA1 locus and carried a homozygous 76C-T HOXA1 mutation resulting in substitution of a stop codon for arginine (R26X; 142955.0003). Tischfield et al. (2005) pointed out that to their knowledge this was the first report of viable homozygous truncating mutations in any human HOX gene and of a mendelian disorder resulting from mutations in a human HOX gene critical for development of the central nervous system.

	ASRT2						
7p15-p14	NOD1, CARD4	Nucleotide-binding oligomerization domain protein 1	605980			REc	
7p15-p14.2	HOXA3, HOX1E	Homeo box-A3	142954		homolog of Drosophila zen1, zen2	RE	6(Hox1.5)
7p15-p14.2	HOXA4, HOX1D	Homeo box-A4	142953		homolog of Drosophila Dfd	A, REa, H, RE	6(Hox1.4)
7p15-p14.2	HOXA5, HOX1C	Homeo box-A5	142952			A, REa, H, RE	6(Hox1.3)
7p15-p14.2	HOXA6, HOX1B	Homeo box-A6	142951			A, REa, H, RE	6(Hox1.2)
7p15-p14.2	HOXA7, HOX1A	Homeo box-A7	142950		homolog of Drosophila Antp	A, REa, H, RE	6(Hox1.1)
7p15-p14.2	HOXA9, HOX1G	Homeo box-A9	142956		homolog of Drosophila Abd-B; fused to NUP98 in myeloid leukemia	RE, Ch	6(Hox1.7)
7p15-p14.2	HOXA10, HOX1H	Homeo box-A10	142957			A, REa, H, RE	
7p15-p14.2	HOXA11, HOX1I	Homeo box-A11	142958	Radioulnar synostosis with amegakaryocytic thrombocytopenia, 605432(3)		A, REa, H, RE	
7p15-p14.2	HOXA11S	Homeo box A11, antisense	607530			REc	6 (Hoxa11s)
7p15-p14.2	HOXA13, HOX1J	Homeo box-A13	142959	Hand-foot-uterus syndrome, 140000 (3); Guttmacher syndrome, 176305(3)		RE, Fd	6 (Hoxa13, Hd)
7p15-p14.2	MIRN196B, MIR196B	Micro RNA 196B	609688			REc	
7p15-p14	AAA1	Asthma-associated alternatively spliced gene 1	608596			REc	

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Search for: HOXB Find Find Next (from the current location)

- Enter gene symbol, chromosomal location, or disorder keyword to search for, e.g. "CYP1", "5", "1pter", "Xq", or "alzheimer".
- You must capitalize X and Y to search for those chromosomes.

17q21-q22, HOXB1 to 17q21-q22, PCTP

<<Move Up Move Down>>

Location	Symbol	Title	MIM #	Disorder	Comments	Method	Mouse
17q21-q22	HOXB1, HOX2I	Homeo box-B1	142968			RE	11 (Hox2.9)
17q21-q22	HOXB2, HOX2H	Homeo box-B2	142967			RE	11 (Hox2.8)
17q21-q22	HOXB3, HOX2G	Homeo box-B3	142966			RE	11 (Hox2.7)
17q21-q22	HOXB4, HOX2F	Homeo box-B4	142965			RE	11 (Hox2.6)
17q21-q22	HOXB5, HOX2A	Homeo box-B5	142960			REa, A, H, Fd, RE	11 (Hox2.2)
17q21-q22	HOXB6, HOX2B	Homeo box-B6	142961			RE	11 (Hox2.2)
17q21-q22	HOXB7, HOX2C	Homeo box-B7	142962			RE	11 (Hox2.3)
17q21-q22	HOXB8, HOX2D	Homeo box-B8	142963			RE	11 (Hox2.4)
17q21-q22	HOXB9, HOX2E	Homeo box-B9	142964			RE	11 (Hox2.5)
17q21-q22	HPC9	Prostate cancer, hereditary, 9	610997	{Prostate cancer, hereditary, 9} (2)	max LOD at D17S1820	Fd	
				Epidermolytic hyperkeratosis, 113800 (3);			

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Search for: HOXC Find Find Next (from the current location)

- Enter gene symbol, chromosomal location, or disorder keyword to search for, e.g. "CYP1", "5", "1pter", "Xq", or "alzheimer".
- You must capitalize X and Y to search for those chromosomes.

12q13, HOXC4 to 12q13, KRT18

<<Move Up Move Down>>

Location	Symbol	Title	MIM #	Disorder	Comments	Method	Mouse
12q13	HOXC4, HOX3E	Homeo box-C4	142974			RE	
12q13	HOXC5, HOX3D	Homeo box-C5	142973			RE	15 (Hox6.2)
12q13	HOXC6, HOX3C	Homeo box-C6	142972			RE	15 (Hox6.1)
12q13	HOXC8, HOX3A	Homeo box-C8	142970			RE	15 (Hox3.1)
12q13	HOXC9, HOX3B	Homeo box-C9	142971			RE	15 (Hox3.2)
12q13	HOXC12, HOX3F	Homeo box-C12	142975			RE	
12q13	HOXC13, HOX3G	Homeo box-C13	142976		fused with NUP98 in AML	RE	
12q13	HPV18I2	Human papillomavirus type 18 integration site-2	167960		on 8 near MYC in HeLa	REa, A	
12q13	HRG1	Heme-responsive gene 1	612187			REc	
12q13	IKZF4, ZNFN1A4, EOS, KIAA1782	Ikaros family zinc finger 4	606239			R, REc	
12q13	ITGA7	Integrin, alpha-7	600536	Myopathy, congenital (3)		A	
12q13	KCNH3, BEC1	Potassium voltage-gated channel, subfamily H (eag-related), member 3	604527			REc	
	KIF5A, NKHC					A, REc	

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Search for: HOXD Find Find Next (from the current location)

- Enter gene symbol, chromosomal location, or disorder keyword to search for, e.g. "CYP1", "5", "1pter", "Xq", or "alzheimer".
- You must capitalize X and Y to search for those chromosomes.

2q31-q32, HOXD3 to 2q31.1-q31.3, PJVK

<<Move Up Move Down>>

Location	Symbol	Title	MIM #	Disorder	Comments	Method	Mouse
2q31-q32	HOXD3, HOX4A	Homeo box-D3	142980			RE	2 (Hox4.1)
2q31-q32	HOXD4, HOX4B	Homeo box-D4	142981	{Leukemia, acute lymphoblastic, susceptibility to} (3)	peak at 2q32.3 by A	A, RE	2 (Hox4.2)
2q31-q32	HOXD9, HOX4C	Homeo box-D9	142982			RE	2 (Hox4.3)
2q31-q32	HOXD10, HOX4D	Homeo box-D10	142984	Vertical talus, congenital, 192950 (3); Charcot-Marie-Toothdisease, foot deformity of (3)		REa, RE	2 (Hox4.4)
2q31-q32	HOXD8, HOX4E	Homeo box-D8	142985			RE	2 (Hox4.5)
2q31-q32	HOXD11, HOX4F	Homeo box-D11	142986			RE	2 (Hox4.6)
2q31-q32	HOXD1, HOX4G	Homeo box-D1	142987			RE	2 (Hox4.7)
2q31-q32	HOXD12, HOX4H	Homeo box-D12	142988		upstream from HOX4A-G	REc	2 (Hox4.8)
2q31-q32	HOXD13, HOX4I, SPD, BDSD	Homeo box-D13	142989	Synpolydactyly, type II, 186000 (3); Brachydactyly, type E, 113300(3); Brachydactyly, type D, 113200 (3); Synpolydactyly with foot anomalies, 186000 (3); Syndactyly, type V, 186300	upstream from HOX4A-G	REc, Fd	2 (Hox4.9)

#186000
SYNPOLYDACTYLY 1; SPD1

GeneTests, Links

Alternative titles; symbols

SYNDACTYLY, TYPE II
SYNPOLYDACTYLY WITH FOOT ANOMALIES, INCLUDED

Gene map locus 2q31-q32

TEXT

A number sign (#) is used with this entry because of evidence that synpolydactyly-1 (SPD1) is caused by mutation in the HOXD13 gene (142989). Synpolydactyly with characteristic foot anomalies is likewise caused by mutation in the HOXD13 gene.

See also SPD2 (608180), caused by mutation in the fibulin-1 gene (FBLN1; 135820) on chromosome 22q13, and SPD3 (610234), which has been mapped to chromosome 14q11.2-q12.

CLINICAL FEATURES

In the hands there is usually syndactyly of the third and fourth fingers associated with polydactyly of all components or of part of the fourth finger in the web. In the feet there is polydactyly of the fifth toe included in a web of syndactyly of the fourth and fifth toes. The most extensive pedigree is that described by Thomsen (1927) showing 31 affected males and 11 affected females in 7 generations. Other kindreds were reported by Alvord (1947) and Pipkin and Pipkin (1946) among others. Cross et al. (1968) observed a kindred with 27 affected persons. Two persons transmitted the gene without showing any effects themselves. All persons with clinically evident malformation in the hand showed anomalous palmar dermatoglyphics. No linkage with any of 12 loci was demonstrable. An excess of affected males has been a consistent feature. Cross et al. (1968) found, in the literature and in their kindred, 133 females and 174 males affected. The 'original' case of Fabry disease (301500) reported by Anderson (1898) had this anomaly: 'The fingers of both hands are contracted at the middle and distal phalanges of the fourth finger on each hand are duplicated, the two digits being enclosed in one cutaneous investment....his mother and sister, and three out of four of his children, had congenital deformities like his own.' Merlob and Grunebaum (1986) found the anomaly in 16 persons in 6 generations of a family.

Seuraavat leikkeet ovat jo vanhoja,
ja uusia "geenivirheitä" on löydetty

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Search for: hoxa Find Find Next (from the current location)

- Enter gene symbol, chromosomal location, or disorder keyword to search for, e.g. "CYP1", "5", "1pter", "Xq", or "alzheimer".
- You must capitalize X and Y to search for those chromosomes.

7p15-p14.2, HOXA1 to 7p14.2, RP9

<<Move Up Move Down>>

Location	Symbol	Title	MIM #	Disorder	Comments	Method	Mouse
7p15-p14.2	HOXA1, HOX1F	Homeo box-A1	142955		homolog of Drosophila lab	RE	6(Hox1.6)
7p15-p14.2	HOXA3, HOX1E	Homeo box-A3	142954		homolog of Drosophila zen1, zen2	RE	6(Hox1.5)
7p15-p14.2	HOXA4, HOX1D	Homeo box-A4	142953		homolog of Drosophila Dfd	A, REa, H, RE	6(Hox1.4)
7p15-p14.2	HOXA5, HOX1C	Homeo box-A5	142952			A, REa, H, RE	6(Hox1.3)
7p15-p14.2	HOXA6, HOX1B	Homeo box-A6	142951			A, REa, H, RE	6(Hox1.2)
7p15-p14.2	HOXA7, HOX1A	Homeo box-A7	142950		homolog of Drosophila Antp	A, REa, H, RE	6(Hox1.1)
7p15-p14.2	HOXA9, HOX1G	Homeo box-A9	142956		homolog of Drosophila Abd-B; fused to	RE, Ch	6(Hox1.7)

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Search for: hoxa Find Find Next (from the current location)

- Enter gene symbol, chromosomal location, or disorder keyword to search for, e.g. "CYP1", "5", "1pter", "Xq", or "alzheimer".
- You must capitalize X and Y to search for those chromosomes.

7p15-p14.2, HOXA1 to 7p14.2, RP9

<<Move Up Move Down>>

Location	Symbol	Title	MIM #	Disorder	Comments	Method	Mouse
7p15-p14.2	HOXA1, HOX1F	Homeo box-A1	142955		homolog of Drosophila lab	RE	6(Hox1.6)
7p15-p14.2	HOXA3, HOX1E	Homeo box-A3	142954		homolog of Drosophila zen1, zen2	RE	6(Hox1.5)
7p15-p14.2	HOXA4, HOX1D	Homeo box-A4	142953		homolog of Drosophila Dfd	A, REa, H, RE	6(Hox1.4)
7p15-p14.2	HOXA5, HOX1C	Homeo box-A5	142952			A, REa, H, RE	6(Hox1.3)
7p15-p14.2	HOXA6, HOX1B	Homeo box-A6	142951			A, REa, H, RE	6(Hox1.2)
7p15-p14.2	HOXA7, HOX1A	Homeo box-A7	142950		homolog of Drosophila Antp	A, REa, H, RE	6(Hox1.1)
7p15-p14.2	HOXA9, HOX1G	Homeo box-A9	142956		homolog of Drosophila Abd-B; fused to NUP98 in myeloid leukemia	RE, Ch	6(Hox1.7)
7p15-p14.2	HOXA10, HOX1H	Homeo box-A10	142957			A, REa, H, RE	
7p15-p14.2	HOXA11, HOX1I	Homeo box-A11	142958	Radioulnar synostosis with amegakaryocytic thrombocytopenia, 605432(3)		A, REa, H, RE	
7p15-p14.2	HOXA11S	Homeo box A11, antisense	607530			REc	6 (Hoxa11s)
7p15-p14.2	HOXA13, HOX1J	Homeo box-A13	142959	Hand-foot-uterus syndrome, 140000 (3); Guttmacher syndrome, 176305(3)		RE, Fd	6(Hoxa13, Hd)
7p15-p14	AS2	Asthma susceptibility 2	608584	{Asthma susceptibility}, 600807 (2)		Fd	
7p15-p14	EVX1	Even-skipped homeo box-1 (homolog of Drosophila)	142996		at 5' end of HOX1 cluster	REn	

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Address http://www.ncbi.nlm.nih.gov/mapview/maps.cgi?ORG=hum&CHR=7&maps=loc-r,morbid,gene&R1=on&query=HOXA6&VERBOSE=ON&ZOOM=3

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7p15.3

7p15.1

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LOC285936		dl	7p15.3	hypothetical protein LOC285936
CHN2	OMIM sv pr dl ev mm hm		7p15.3	chimerin (chimaerin) 2
HOXA1	OMIM sv pr dl ev mm hm		7p15.3	homeo box A1
LOC246724		dl	7p15	DNA directed RNA polymerase II polypeptide J-related gene
AHR	OMIM sv pr dl ev mm hm		7p15	aryl hydrocarbon receptor
TRGC2	sv	dl ev mm	7p15	T cell receptor gamma constant 2
TRGC1	sv	dl ev mm	7p15	T cell receptor gamma constant 1
MYCLK1	OMIM	dl	7p15	v-myc myelocytomatosis viral oncogene homolog (avian)-like 1
TRGV9	sv	dl ev mm	7p15	T cell receptor gamma variable 9
TRGV8	sv	dl ev mm	7p15	T cell receptor gamma variable 8
TRGV5	sv	dl ev mm	7p15	T cell receptor gamma variable 5
TRGV4	sv	dl ev mm	7p15	T cell receptor gamma variable 4
TRGV3	sv	dl ev mm	7p15	T cell receptor gamma variable 3
TRGV2	sv	dl ev mm	7p15	T cell receptor gamma variable 2
TRGJP2	sv	dl ev mm	7p15	T cell receptor gamma joining P2
TRGJP1	sv	dl ev mm	7p15	T cell receptor gamma joining P1
TRGJP	sv	dl ev mm	7p15	T cell receptor gamma joining P
TRGJ2	sv	dl ev mm	7p15	T cell receptor gamma joining 2
TRGJ1	sv	dl ev mm	7p15	T cell receptor gamma joining 1
LOC285943		dl	7p15.2	hypothetical protein LOC285943
LOC285944		dl	7p15.2	hypothetical protein LOC285944
LOC340281		dl	7p15.2	hypothetical protein LOC340281
KIAA0087		pr dl	7p15.2	KIAA0087 gene product
HOXA6	OMIM sv pr dl ev mm hm		7p15-p14	homeo box A6
CREB5	sv pr dl ev mm hm		7p15	cAMP responsive element binding protein 5
LOC222159		dl	7p15.1	hypothetical protein LOC222159
LOC285949		dl	7p15.1	hypothetical protein LOC285949
YKT6	OMIM sv pr dl ev mm hm		7p15.1	SNARE protein Ykt6
NPY	OMIM sv pr dl ev mm hm		7p15.1	neuropeptide Y

View Summary:

Track 1: Genes On Sequence — Table View

Region Displayed: **24M-29Mbp** Download/View Sequence/Evidence

Total Genes On Chromosome: **1383** [8 not localized]

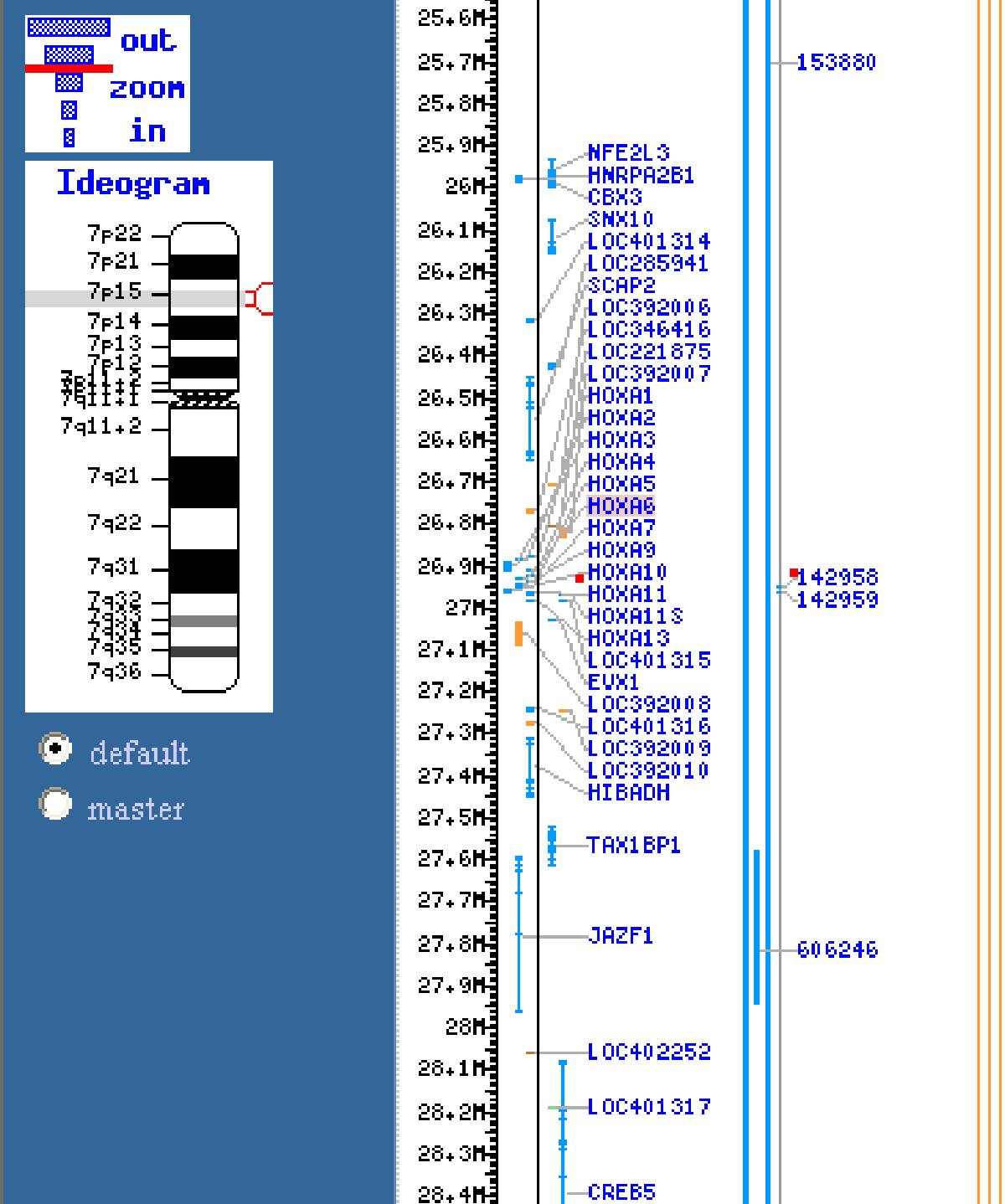
Genes Labeled: **48** Total Genes in Region: **48**

Track 2: OMIM Morbid — Table View

Region Displayed: **7p15.3-7p15.1**

http://www.ncbi.nlm.nih.gov/mapview

Internet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7p21
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LOC401317
CREB5

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1: NT_007819. Homo sapiens chro...[gi:37538470]

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Search for gene Find

- CDS with gene and mRNA
- gene, tRNA, promoter...
- Other features
- Hide sequence

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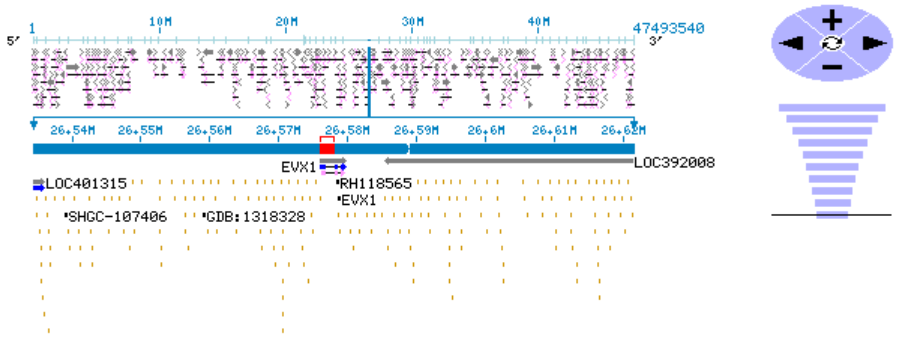

Legend:

segment boundaries – CDS – RNA – gene
region/SNP – other feature
– sequence fragment shown

Sequence:

26576011 GCAATGGGGC TTCCTCCCAG AGGCGGTGCG GCACAGAGGA GCGCTCGCTT CACAAGGTGA
EVX1 mRNA-eve, even-

26576071 CCCTAGCTCC CACCGCCACC GCCGCGGTCG CGGTCCAGAC CGCGCTCCAG CAGCTCCGCG
EVX1 mRNA-eve, even-

dbSNP:2074399

26576131 CCCTCCCAGG CACCCGGCCT TTCTTTCTCC CTCTTGCAAC CAAGATCCGT CCGGCCGCTG
EVX1 mRNA-eve, even-

26576191 GAGACCCAGG GAGCCGGGGT TAGGAACTCA CTTGGGGCTT TCCCCTCCCC CACCGGAGAG
EVX1 mRNA-eve, even-

26576251 CCCCGGGATG GAGAGCCGAA AGGACATGGT TGTGTTTCTG GATGGGGGTC AGCTTGGCAC
EVX1 mRNA-eve, even-

M E S R K D M V V F L D G G Q L G T
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26576311 TCTGGTTGGC AAGAGAGTCT CAAATTTGTC CGAAGCCGTG GGCAGCCCGC TGCCGGAGCC
EVX1 mRNA-eve, even-

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Search for: hoxb Find Find Next (from the current location)

- Enter gene symbol, chromosomal location, or disorder keyword to search for, e.g. "CYP1", "5", "1pter", "Xq", or "alzheimer".
- You must capitalize X and Y to search for those chromosomes.

17q21-q22, HOXB1 to 17q21-q22, SHCL1

<<Move Up Move Down>>

Location	Symbol	Title	MIM #	Disorder	Comments	Method	Mouse
17q21-q22	HOXB1, HOX2I	Homeo box-B1	142968			RE	11 (Hox2.9)
17q21-q22	HOXB2, HOX2H	Homeo box-B2	142967			RE	11 (Hox2.8)
17q21-q22	HOXB3, HOX2G	Homeo box-B3	142966			RE	11 (Hox2.7)
17q21-q22	HOXB4, HOX2F	Homeo box-B4	142965			RE	11 (Hox2.6)
17q21-q22	HOXB5, HOX2A	Homeo box-B5	142960			REa, A, H, Fd, RE	11 (Hox2.2)
17q21-q22	HOXB6, HOX2B	Homeo box-B6	142961			RE	11 (Hox2.2)
17q21-q22	HOXB7, HOX2C	Homeo box-B7	142962			RE	11 (Hox2.3)
17q21-q22	HOXB8, HOX2D	Homeo box-B8	142963			RE	11 (Hox2.4)
17q21-q22	HOXB9, HOX2E	Homeo box-B9	142964			RE	11 (Hox2.5)
				Epidermolytic hyperkeratosis, 113800 (3); Nevus, epidermal epidermolytic	in cluster		

The OMIM Gene map presents the cytogenetic map location of disease genes and other expressed genes described in OMIM. See the OMIM Morbid Map for a list of disease genes organized by disease. For more refined maps of genes and DNA segments click on the **Location** to invoke NCBI Entrez Map Viewer.

Search for: hoxc Find Find Next (from the current location)

- Enter gene symbol, chromosomal location, or disorder keyword to search for, e.g. "CYP1", "5", "1pter", "Xq", or "alzheimer".
- You must capitalize X and Y to search for those chromosomes.

12q13, HOXC4 to 12q13, METTL1

<<Move Up Move Down>>

Location	Symbol	Title	MIM #	Disorder	Comments	Method	Mouse
12q13	HOXC4, HOX3E	Homeo box-C4	142974			RE	
12q13	HOXC5, HOX3D	Homeo box-C5	142973			RE	15 (Hox6.2)
12q13	HOXC6, HOX3C	Homeo box-C6	142972			RE	15 (Hox6.1)
12q13	HOXC8, HOX3A	Homeo box-C8	142970			RE	15 (Hox3.1)
12q13	HOXC9, HOX3B	Homeo box-C9	142971			RE	15 (Hox3.2)
12q13	HOXC12, HOX3F	Homeo box-C12	142975			RE	
12q13	HOXC13, HOX3G	Homeo box-C13	142976		fused with NUP98 in AML	RE	
12q13	HPV18I2	Human papillomavirus type 18 integration site-2	167960		on 8 near MYC in HeLa	REa, A	
12q13	ITGA7	Integrin, alpha-7	600536	Myopathy, congenital (3)		A	
				Epidermolytic hyperkeratosis, 113800 (3);			

The OMIM Gene map presents the cytogenetic map location of disease genes and other expressed genes described in OMIM. See the OMIM Morbid Map for a list of disease genes organized by disease. For more refined maps of genes and DNA segments click on the **Location** to invoke NCBI Entrez Map Viewer.

Search for: hoxd Find Find Next (from the current location)

- Enter gene symbol, chromosomal location, or disorder keyword to search for, e.g. "CYP1", "5", "1pter", "Xq", or "alzheimer".
- You must capitalize X and Y to search for those chromosomes.

2q31-q32, HOXD3 to 2q32, DLX1

<<Move Up Move Down>>

Location	Symbol	Title	MIM #	Disorder	Comments	Method	Mouse
2q31-q32	HOXD3, HOX4A	Homeo box-D3	142980			RE	2 (Hox4.1)
2q31-q32	HOXD4, HOX4B	Homeo box-D4	142981		peak at 2q32.3 by A	A, RE	2 (Hox4.2)
2q31-q32	HOXD9, HOX4C	Homeo box-D9	142982			RE	2 (Hox4.3)
2q31-q32	HOXD10, HOX4D	Homeo box-D10	142984			REa, RE	2 (Hox4.4)
2q31-q32	HOXD8, HOX4E	Homeo box-D8	142985			RE	2 (Hox4.5)
2q31-q32	HOXD11, HOX4F	Homeo box-D11	142986			RE	2 (Hox4.6)
2q31-q32	HOXD1, HOX4G	Homeo box-D1	142987			RE	2 (Hox4.7)
2q31-q32	HOXD12, HOX4H	Homeo box-D12	142988		upstream from HOX4A-G	REc	2 (Hox4.8)
2q31-q32	HOXD13, HOX4I,	Homeo box-D13	142989	Synpolydactyly, type II, 186000 (3)	upstream from	REc,	2

HOMEO BOX A11; HOXA11

Alternative titles; symbols

HOMEO BOX 1I; HOX1I

Thompson and Nguyen (2000) observed 2 families with autosomal dominant inheritance of radioulnar synostosis in association with amegakaryocytic thrombocytopenia (605432).

Because HOXA10 and HOXA11 are involved in forearm morphogenesis, and HOXA10 is expressed in megakaryocytic bone marrow precursor cells, Thompson and Nguyen (2000) studied these genes in this family. They found that the fathers and affected children were **heterozygous** for a single nucleotide deletion in a highly conserved region in exon 2 encoding the homeodomain of HOXA11 (142958.0001). The authors stated that this was the first reported germline HOX gene mutation associated with a human nonneoplastic hematologic disorder, and only the third HOX gene implicated in a human syndrome, the others being HOXD13 in synpolydactyly (142989) and HOXA13 in hand-foot-genital syndrome (142959).

HOMEO BOX A13; HOXA13

Alternative titles; symbols

HOMEO BOX 1J; HOX1J

HAND-FOOT-GENITAL SYNDROME [HOXA13, TRP369TER]

Mortlock and Innis (1997) found that patients with the hand-foot-genital syndrome (140000) in the family reported by Stern et al. (1970) had an **A-to-G transition in a highly conserved tryptophan codon** in the HOXA13 homeodomain, which, in addition to causing a **trp369-to-ter substitution** (TGG to TGA), also destroyed a NlaIV restriction site. The nonsense mutation was predicted to produce a **truncated protein missing 20 C-terminal amino acids** based on homology to other homeodomains whose 3-dimensional structures had been determined. This portion of the normal homeodomain folds into the last of the 3 alpha-helices. **This helix is critical for DNA binding.**

The authors noted that the tryptophan that was mutated in this family is the only amino acid which is invariant in all known homeodomain proteins.

HOMEO BOX D13; HOXD13

Alternative titles; symbols

HOMEO BOX 4I; HOX4I

See HOXD12 (142988). Muragaki et al. (1996) sequenced the HOXD13 gene and determined that the 5-prime region of the HOXD13 protein contains 2 serine stretches and 1 alanine stretch. Amplification of the gene region encoding the alanine stretch showed an additional larger band in the affected individuals in 3 pedigrees with synpolydactyly (186000). Muragaki et al. (1996) noted that the mutation found in these pedigrees did not disrupt an evolutionarily conserved domain.

Akarsu et al. (1996) analyzed the genomic structure of the HOXD13 gene. They determined that it consists of 2 exons and that it encodes a polypeptide of 335 amino acids which has high homology to the chicken Hoxd13 gene. Akarsu et al. (1996) reported that the more 3-prime exon encodes the highly conserved homeodomain sequences and that the upstream 757-bp exon and the downstream 248-bp exon are separated by an intron of 950 bp, within which lies a stretch of polymorphic CA repeat sequences. They noted that the **5-prime end of the gene contains 15 alanine residues**. Akarsu et al. (1996) reported that in 2 unrelated Turkish families with synpolydactyly (186000), **duplication of 9 residues** of this polyalanine tract (142989.0001) was transmitted from affected parents to their affected offspring but not to their unaffected offspring. This duplication was also found in 2 affected individuals who were recombinant for the HOXD13 CA repeat polymorphism.

On muitakin *Drosophilan* kehitysgeenejä, jotka toimivat ihmisessäkin. Joskus niistä tunnetaan mutaatioita (= vaivoja), joskus ei

Vaivattomuus viittaa niin keskeiseen toimintaan, että alkio kuolee anivarhain

Mutations in the human ortholog of *Aristaless* cause X-linked mental retardation and epilepsy

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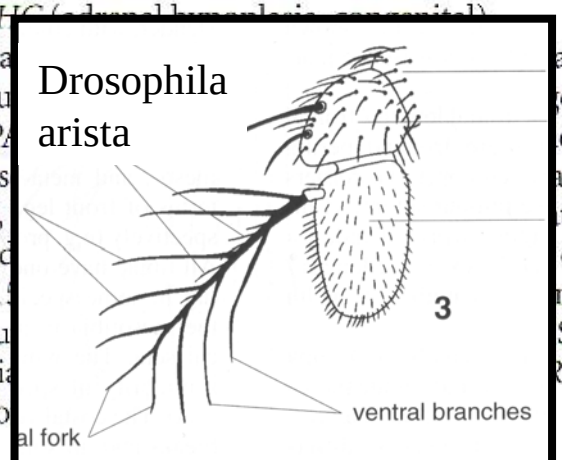
Mental retardation and epilepsy often occur together. They are both heterogeneous conditions with acquired and genetic causes. Where causes are primarily genetic, major advances have been made in unraveling their molecular basis. The human X chromosome alone is estimated to harbor more than 100 genes that, when mutated, cause mental retardation[1]. At least eight autosomal genes involved in idiopathic epilepsy have been identified[2], and many more have been implicated in conditions where epilepsy is a feature. We have identified mutations in an X chromosome–linked, *Aristaless*-related, homeobox gene (*ARX*), in nine families with mental retardation (syndromic and nonspecific), various forms of epilepsy, including infantile spasms and myoclonic seizures, and dystonia. Two recurrent mutations, present in seven families, result in expansion of polyalanine tracts of the ARX protein. These probably cause protein aggregation, similar to other polyalanine[3] and polyglutamine[4] disorders. In addition, we have identified a missense mutation within the *ARX* homeodomain and a truncation mutation. Thus, it would seem that mutation of *ARX* is a major contributor to X-linked mental retardation and epilepsy.

West syndrome consists of infantile spasms, an electroencephalogram pattern of hypsarrhythmia and subsequent mental retardation. The etiology is heterogeneous and, for the most part, unknown[5,6]. An X-linked subgroup[7] of West syndrome was recently identified (ISSX, MIM 308350). The 'causative' gene was mapped[8] to a region of approximately 7 Mb between *DXS1226* and *AHC*

Preliminary tra ated the
presence of abou enomic
sequence of the P *POLA*
(DNA polymeras te gene
underlying ISSX, ttern in
fetal, infant and clusters
Hs.257648, Hs.1 ned for
mutations in fou SSX[8–10]
and one Norwegi *RX* were
detected in four o



EVEN-SKIPPED HOMEO BOX 1; EVX1

HOMEO BOX EVX-1

Faiella et al. (1991) isolated and mapped the human equivalent of the Drosophila EVX1 gene. The gene encodes a protein of 407 amino acids containing a homeodomain closely related to the *Drosophila* even-skipped (eve) segmentation gene of the pair-rule class. EVX1 belongs to a small family of vertebrate eve-related homeo box genes including human EVX1 and EVX2 (142991), their murine homologs Evx-1 and Evx-2, and the frog Xhox-3 gene. The human EVX2 gene is located at the 5-prime end of the HOX4 locus on chromosome 2 (see HOXD13; 142989). Faiella et al. (1991) showed that the EVX1 gene is located at the 5-prime end of the HOX1 locus (see HOXA1; 142955) on chromosome 7, 48 kb upstream from the most 5-prime of the 11 HOX1 genes, namely HOX1J (HOXA13; 142959). Both EVX genes are transcribed in an opposite orientation as compared to adjacent HOX genes.

EVEN-SKIPPED HOMEO BOX 2; EVX2

HOMEO BOX EVX-2

Genetic analysis of early embryogenesis in Drosophila provided insight into the molecular events controlling body plan formation; in particular, the process of segmentation and the specification of segment identification was shown to be controlled by a limited number of genes. These genes exist in several homeo box families that encode homeo domains with different primary sequences. For example, Drosophila homeo domains belong to at least 7 classes, including Antennapedia (see 142950), engrailed (see 131290, 131310), and even-skipped (eve). Murine homologs of most Drosophila homeo domain classes have been described. In particular, Bastian and Gruss (1990) reported 2 murine genes containing an eve-type homeo box, evx-1 (142996) and evx-2. The evx-1 expression pattern during mouse embryogenesis was considered consistent with a role in establishing the anterioposterior embryonic axis. D'Esposito et al. (1991) demonstrated an Evx-2-type of homeo box on human chromosome 2, 13 kb upstream from HOX4I (142989). That the EVX2 sequences belong to an active gene was indicated by the fact that they are transcribed and properly processed in cells and tissues. The human EVX2 homeo box is homologous to the Drosophila eve homeo box identified by Macdonald et al. (1986). In all, 9 homeo boxes are included in a 100-kb region of DNA on the long arm of human chromosome 2. Bastian et al. (1992) demonstrated that the murine 'even-skipped-like' gene Evx-2 is closely linked to the Hox-4 complex in that species also, but is transcribed in the opposite direction.

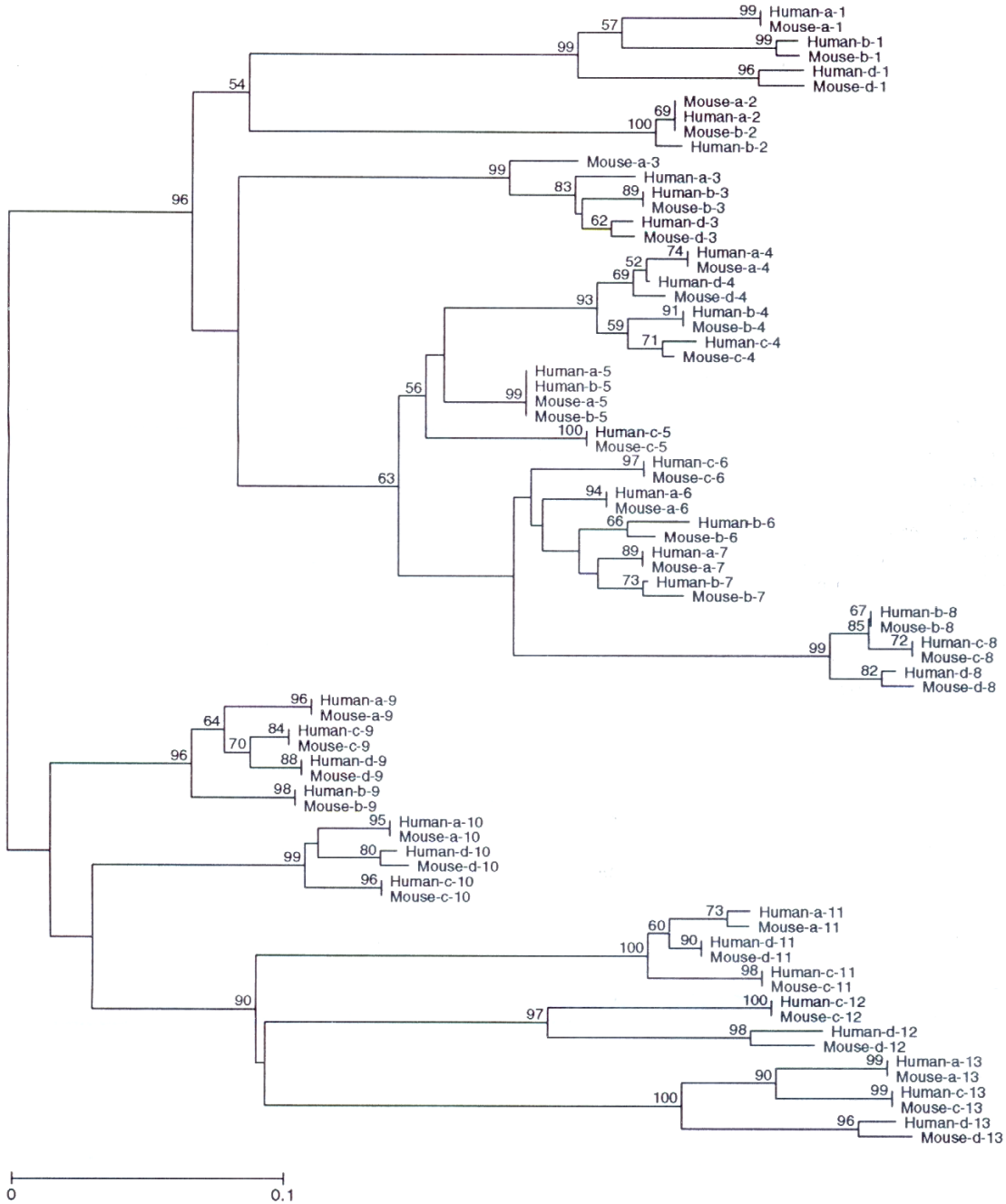
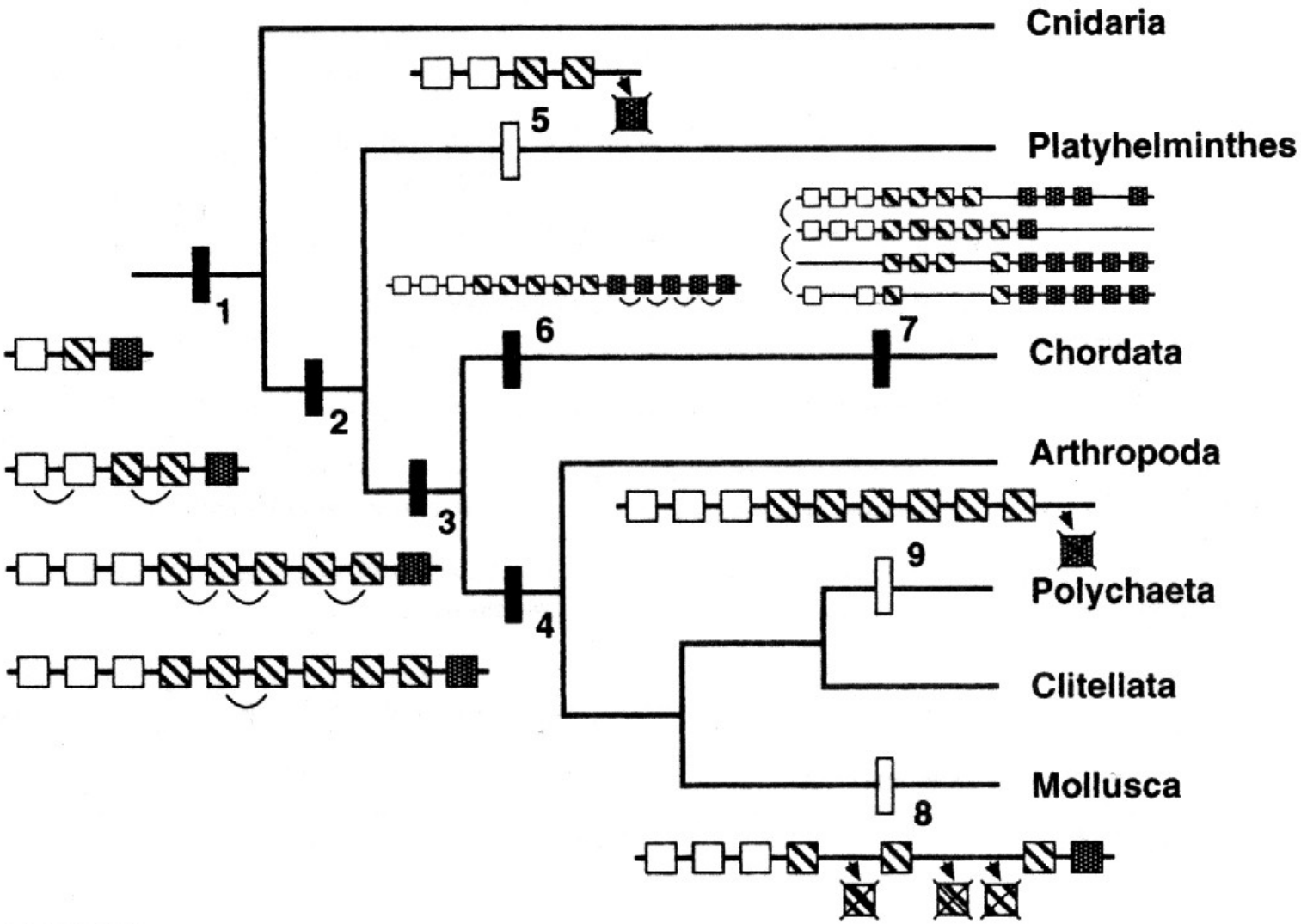


FIGURE 3.—Phylogenetic tree of 76 human and mouse *Antp*-class homeobox genes.



LEGEND

3'-group genes
central-group genes
5'-group genes
gene duplication
gene loss
cluster duplication