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HOMEOTIC GENES AND THE HOMEOBOX

W. J. Gehring and Y. Hiromi

Department of Cell Biology, Biocenter, University of Basel, Klingelbergstrasse 70, Switzerland

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INTRODUCTION

The term "homeosis" (originally spelled "homoeosis") was proposed by Bateson (8) to describe the transformation of one structure of the body into the homologous structure of another body segment. Homeotic transformation can result, for example, from abnormal regeneration of amputated structures (epigenetically) or from germ-line mutations. In *Drosophila* and some other insects a large number of mutants have been described that transform part of a body segment, or an entire body segment, into the corresponding part of another segment. In the *Antennapedia (Antp)* mutant of *Drosophila*, for

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example, the antennae on the head of the fly are transformed into an additional pair of second legs. Apparently, the *Antp*$^+$ allele ensures that the pair of second legs are formed only in the second thoracic segment. Thus, homeotic genes like *Antp* are involved in specifying the spatial organization (body plan) of the developing animal. Since the formation of even a single structure (such as a leg) requires the concerted action of many hundreds or thousands of genes, the homeotic genes are thought to be master control genes that regulate other genes and program certain developmental pathways. Since each of the homeotic genes is specifically required for the formation of one, or a few, body segments, Lewis (99) has advanced the hypothesis that homeotic genes specify segment diversity. Primitive arthropods (e.g. myriapods) consist of a series of largely identical body segments, which are significantly modified only in the head and the last abdominal segments. In the course of evolution leading to higher insects the various body segments diversified to a large extent and acquired different functions. The homeotic genes are thought to be control genes that specify the unique identities of each of the segments. In *Drosophila* the homeotic genes are clustered primilary in two chromosomal regions, the Antennapedia (ANT-C) and Bithorax (BX-C) complexes. Since these genes are thought to select a certain developmental pathway they have also been designated "selector" genes (34, 35). Genes in the BX-C are postulated to have evolved by tandem duplication from an ancestral gene followed by mutations (99). Recent molecular studies indicate that in fact homeotic genes constitute a gene family that shares a common DNA sequence element, termed the "homeobox" (36, 108). It is not clear at the moment whether during evolution the individual genes arose by tandem duplication, by exon shuffling, or by some other mechanism.

At least three classes of genes have been shown to contribute to the establishment of the body plan. These classes contain (*a*) the maternal genes, which are expressed during oogenesis and specify the polarity or the spatial coordinates of the egg and the developing embryo; (*b*) the segmentation genes, which are expressed zygotically (after fertilization), and specify the number and polarity of the body segments; and finally (*c*) the homeotic genes, which presumably specify segment identity. This review concentrates largely on homeotic genes, since there has been rapid progress in this area and since the genetics of *Drosophila* embryogenesis was recently reviewed (105). The genes involved in sex determination are not included in this review, although it can be argued that mutants such as *transformer* and *double sex* that transform male genitalia into female genitalia and vice versa may be regarded as homeotic mutations, as the male and female genitalia derive from different segments (120). This review concentrates on *Drosophila* because most of the analyses have been performed in this organism, but some recent data on homeotic genes and homeoboxes in other organisms are included. (For recent reviews of specific topics see 1, 4, 36, 37, 59, 86, 88, 96, 100, 123, 138).

PHENOTYPIC EFFECTS OF HOMEOTIC MUTATIONS

Homeotic mutations, as mentioned, lead to the replacement of part of a body segment or an entire segment by the homologous structures from another segment. In *Drosophila melanogaster* the homeotic genes are largely confined to ANT-C and BX-C, which are located on the right arm of the third chromosome. A list of the major genes found in these two clusters, as well as some of the genes located outside them, is given in Table 1, which also summarizes the phenotypic effects of the mutations. The mutants are listed in their proximal-to-distal order. Interestingly, the genes are expressed in essentially the same anteroposterior order in the animal as they are arranged along the chromosome (99) (compare Table 1 with Figure 1). The reasons for this arrangement are not known. The genes may have arisen by tandem duplication in the course of evolution leading to such an arrangement, but in addition there are functional interactions in cis, between the genes (see below), which may prevent the dispersion of the homeotic gene clusters.

Two fundamentally different types of mutations that lead to opposite kinds of transformation have been found in homeotic genes: the recessive loss-of-function mutants, which abolish gene function and as a rule lead to the transformation of one segment into a more anterior one, and the dominant gain-of-function mutants, which generally lead to posterior transformations. In well-defined cases the recessive loss of function is due to the deletion of the gene. However, in many cases deletions have been used that include several genes or transcription units, so that more than one parameter is changed simultaneously, and the results are difficult to interpret. Furthermore, as a consequence of the deletion, new flanking sequences become juxtaposed to the adjacent gene in the cluster, which may influence its expression. Therefore, several mutations, particularly those caused by chromosome rearrangements such as inversions and translocations, produce both recessive loss- and dominant gain-of-function phenotypes.

The dominant gain-of-function mutations are more difficult to interpret, but there is growing evidence that they are due to overexpression of the gene product at ectopic sites (see below). The dominant effects of such mutations can be abolished by deletion of the gene (pseudorevertants). The *Antp* gene can be mutated such that it gives rise to several different dominant gain-of-function phenotypes. The best-characterized phenotype is the transformation of the antenna toward a second leg. The mutation *Cephalothorax (Ctx),* which results from a complex chromosome rearrangement, leads to a transformation of the posterior head region towards the mesothorax (136). The dominant mutations *Extra sex combs (Scx)* and *Humeral (Hu)* may also be allelic to *Antp* (51), although this is difficult to prove, since there is no conclusive genetic test for allelism of dominant mutants. *Scx* transforms the second and third legs toward first legs, and *Hu* generates extra bristles, whose identity is

Table 1 Phenotype of the major loss of function mutants of the *Antennapedia* and *Bithorax* complexes

Gene	Symbol	Phenotype (loss of function)[a]	Homeobox	References
Antennapedia Complex	ANT-C			
labial	*lab*	derivatives of labial segment missing	?	71
proboscipedia	*pb*	labial palps → first leg (T1); → antenna	?	73
zerknüllt	*zen*	failure to form a normal optic lobe and to undergo head involution	?	161
Deformed	*Dfd*	eyes reduced, antennae and maxillary palps partly duplicated	+	159
Sex combs reduced	*Scr*	labial → maxillary segment, T1 → T2	+	146,160
fushi tarazu	*ftz*	lacks alternating "parasegments"	+	161
Antennapedia	*Antp*	T2, T3 → T1 and head	+	71,134,160
Bithorax Complex	BX-C			
Ultrabithorax	*Ubx*	T2p to Ala → "T2 + T2" (= T1p T2a) (parasegments 5+6→4+4)	+	18,99,100,130

anterobithorax	*abx*	T2p → T1p T3a → T2a			10,18,99
bithorax	*bx*	T3a → T2a			99,100,129
bithoraxoid	*bxd*	A1a → T3a			77,99,100
postbithorax	*pbx*	T3p → T2p			99,100
infra-abdominal-2	*iab-2*	A2 → A1	(= abd A)	+	68,82,157
infra-abdominal-3	*iab-3*	A3–A6 → A2			
infra-abdominal-4	*iab-4*	A4 → A3	loss of gonads		
infra-abdominal-5	*iab-5*	A5,A6 → A4			
infra-abdominal-6	*iab-6*	A6,A7 → A5			
infra-abdominal-7	*iab-7*	A8 → A7	(= Abd B)	+	
infra-abdominal-8	*iab-8*	A8 → A7			
Outsiders					
caudal	*cad*	(expressed in A9 and A10) no mutation available		+	114
engrailed	*en*	posterior compartment formation of all segments		+	30,69,80,89, 115,125

[a]T = Thoracic segment; A = Abdominal segment; a = anterior, and p = posterior.

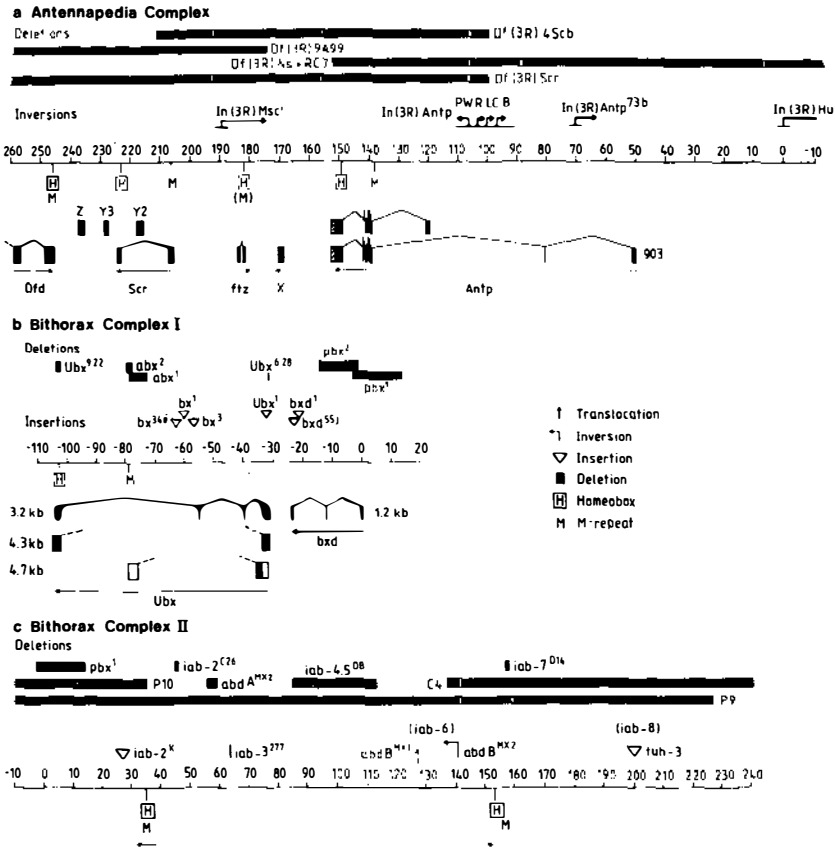

Figure 1 Genetic and DNA map of the two major clusters of homeotic genes in *Drosophila melanogaster*. (a) Antennapedia complex: The symbols are explained in the figure. The DNA coordinates are indicated in kilobases. The transcripts are indicated by black bars (exons) connected by thin lines (introns). The direction of transcription is indicated by a horizontal arrow. The centromere is on the left of the telomere towards the right. (b) *Bithorax Complex* I (*Ubx* domain). (c) Bithorax Complex II (Abdominal domain). The mutant symbols are listed in Table 1.

unknown, on the humerus. In this connection it should be noted that the *Antp*$^+$ gene is strongly expressed in the dorsal prothoracic (humeral) imaginal disc of wild-type larvae (94). The dominant gain-of-function mutants in the BX-C also give rise to transformations in the posterior direction; for example, the mutants *Contrabithorax (Cbx)* and *Haltere-mimic (Hm)* transform the wings (T2) into halteres (T3) (17, 97).

It has been proposed that homeotic transformations are not confined to segments but rather to units consisting of the posterior compartment of one

segment and the anterior compartment of the next segment (49, 61, 76, 81, 107, 118, 147). These metameric units that span a segmental boundary are called "parasegments" (107). On morphological and genetic grounds it appears that the parasegmental boundaries form prior to the segmental ones. The fact that each of the compartments is a polyclone derived from a group of founder cells (87) implies that the transformations are cell-lineage specific. This implication is supported to some extent by in situ hybridization data for the localization of homeotic transcripts and immunolocalization of homeotic proteins (see below). However, some of the mutants of the BX-C respect normal segment boundaries (68).

Homeotic transformations are most conspicuous in the epidermal structures of the larva and the adult fly. The larval cuticle contains denticles and tiny sense organs, which form as segment-specific pattern. In the adult cuticle numerous bristles, trichomes, and sensory organs provide excellent morphological markers and allow resolution down to the single-cell level. The problem that many of the mutations are lethal can be overcome in various ways. In all known cases the embryo with the lethal mutation still develops into a first-instar larva that does not hatch. Cuticle preparations of such larvae provide enough structural information to identify the segments.

In order to study the effect of embryonic lethal mutations on adult structures, clones of homozygous mutant cells can be generated at various stages of development by inducing mitotic recombination in heterozygous animals. The homozygous mutant cells can then be identified on the basis of genetic markers on the adult cuticle or in the interior organs. Alternatively, the imaginal discs can be transplanted from a homozygous mutant embryo or larva to a normal host, and the resulting adult cuticular structures can be analyzed after metamorphosis of the host. Such genetic mosaics have provided evidence for cell autonomy of homeotic-gene expression (98, 117; see also 13). For example, a clone of *bx* mutant cells in the anterior haltere (T3a) is entirely transformed into wing cells (T2a), although it is surrounded by wild-type haltere cells. These studies show that there is no significant transfer of bx^+ product from cell to cell. From the time of induction of the clones, it can be concluded that bx^+ is required from early embryonic stages, throughout development, until metamorphosis when the epidermal cells differentiate terminally. Thus, the continued expression of bx^+ is required to maintain the state of determination, i.e. to keep the cells on a certain developmental path.

Although transformation of the epidermis has been emphasized because of its dramatic phenotype, accumulating evidence indicates that mutations in homeotic genes also affect internal organs, such as the nervous system and the muscles. In the past, detection of transformation in the central nervous system (CNS) was hampered by the paucity of appropriate neuronal markers for segment identity. However, recent identification of segment-specific charac-

teristics in the CNS has led to the conclusion that the CNS is indeed transformed in homeotic mutants, at least by those of the BX-C (39, 40, 65, 153, 154). Furthermore, transformed neuromeres of the CNS can influence axonal growth, such that an axon descending from the nontransformed brain branches at the "wrong" segment (156).

Less evidence is available for transformation of the mesoderm (86). The requirements for the formation of a homeotically transformed muscle are rather stringent, because not only must transformed muscle precursor cells be present, but also proper attachment sites must be provided. Four-winged adult *(bx pbx/Ubx)* flies in which T3 is transformed into T2 do not develop indirect flight muscles in the transformed segment. This appears to be at least partly because in parasegment 5 *Ubx* is expressed only in ectoderm and not in the mesoderm (5). The only known example of muscle transformation is that of an abdominal muscle in the *iab-5* mutation, which has been shown to be independent of the genotype of the cuticle (90). It should be noted that, in contrast to transformations of the epidermis, cell-autonomous transformation has not been demonstrated for the internal structures (but see 91). However, given the fact that homeotic genes are strongly expressed in the CNS and the mesoderm (see below), it is likely that they are also required autonomously in the CNS and possibly in the muscles.

Clonal analysis and pole-cell-transplantation experiments reveal that homeotic selector genes are not required in the germ line (75, 92). However, the homeobox-containing gene *caudal (cad)* is expressed in the germ cells of the larval gonads, although its transcripts have not been detected in the pole cells, i.e. the primordial germ cells (M. Mlodzik & W. J. Gehring, unpublished). The significance of these transcripts in the germ line is currently unknown.

GENETIC AND MOLECULAR ORGANIZATION

The structural complexity of the homeotic genes, and their mutual interaction, makes it necessary to combine classical genetic studies with molecular analysis.

The Antennapedia Complex

Numerous studies have been devoted to the genetic analysis of the Antennapedia complex (23, 70–74, 101, 102, 133, 134, 143, 144, 146, 160, 161). And the distal region spanning 260 kb of DNA between *Deformed (Dfd)* and *Antp* has been cloned (33, 84, 136). The structure of the *Antp* gene has been analyzed in detail (135). The gene is composed of two promoters, eight exons spanning more than 100 kb, and two termination-processing regions (Figure 1, section *a*). Four major transcripts were found, two of which start at

an internal promoter in front of the third exon. The largest intron spans about 60 kb. The transcripts have unusually long leader and trailer sequences of 1-to-2 kb. Despite the complex transcriptional organization, the open-reading frame that starts in exon 5 is the same in all 4 transcripts. The exon nearest the 3' end contains a homeobox, a 180-bp DNA segment shared by many homeotic genes (108, 109, 137). The Antp protein contains stretches of polyglutamin encoded by a repeat of CAG/A, called the "M-repeat" (108). The M-repeat is present in some 200 copies per genome and has also been found in the *Notch* gene, where it was called *opa* (166). The *Antp* locus is defined by deletions; heterozygotes for the two overlapping deletions Ns^{+RC7} and 4SCB (Figure 1, see *a*) that remove only the *Antp* transcription unit show the recessive loss-of-function phenotype, i.e. the anterior transformation of T2 and T3 toward T1 and head structures (W. J. Gehring, unpublished results). The inversions whose breakpoints are indicated in Figure 1, part *a*, show a dominant gain-of-function phenotype that leads to the transformation of the antennae into second legs.

Several other genes within the ANT-C have also been analyzed in some detail (Figure 1). The adjacent gene *X* has so far only been identified as a transcription unit and has not been defined by mutation (84). It encodes a 0.5-kb transcript that is only detected at early embryonic stages between the blastoderm stage and gastrulation. The transcripts accumulate in the anterior-thoracic and posterior-head segments (Figure 2, section *a*), suggesting a role in determining the spatial organization of the embryo. The next gene in the complex, *fushi tarazu (ftz),* is transcribed in the opposite direction relative to its neighbors (83, 84, 163). On the basis of its mutant phenotype (161) it is doubtful whether *ftz* is a homeotic gene, although it can mutate to a dominant gain-of-function phenotype that is postbithroax-like and involves a transformation of the posterior metathoracic segment (T3p) toward posterior mesothorax (T2p) (71, 85; I. Duncan, personal communication). The ftz^- phenotype corresponds to phenotypes of the "pair-rule" mutants, in which alternating body segments are deleted and the remaining segments are fused. (The Japanese name "fushi tarazu" means "less than the normal number of segments.") The sections that are deleted in the ftz^- embryos do not correspond to segments, since they overlap segmental boundaries. They may correspond to parasegments, but the phenotype is somewhat variable, and the deleted sections do not exactly coincide with the anterior/posterior compartment boundary (148). The coding region of *ftz* is only 2-kb long and consists of two exons separated by a 200-bp intron. The 3'-exon contains a homeobox, but there is no well-defined M-repeat. The 5'-flanking sequences contain an unusually long control region of 6.1 kb, in which three functional domains have been localized (52).

The *Sex combs reduced (Scr)* locus consists of at least two exonic regions

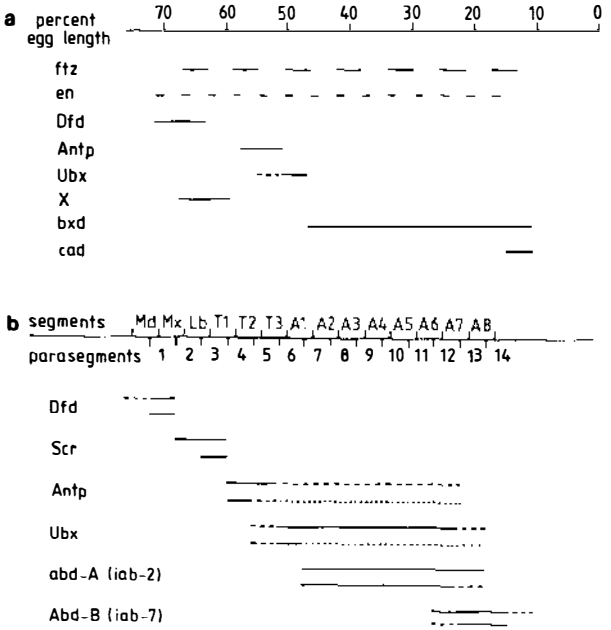

Figure 2 Spatial pattern of homeotic gene expression. (a) Blastoderm stage. (b) Upper line: Germ-band extension stage, lower line: Ventral nervous system after retraction of the germ band. Solid lines indicate region of most prominent expression. Dashed and dotted lines represent regions of weaker expression. The sites of expression of the *en* gene in the anterior-head region are not indicated. The mutant symbols are explained in Table 1.

separated by a large intron (84) and is defined by deletions. It contains both a homeobox and an M-repeat. The apparent loss-of-function phenotype *(Scr^-)* is unusual in that it comprises both an anterior transformation of labial into maxillary structures, as well as a posterior transformation of T1 toward T2 (146, 160). Y2, Y3, and Z are transcripts that remain to be analyzed. The *Dfd* locus also contains a homeobox and an M-repeat (108, 126). Both revessive and dominant *Dfd* alleles have been described that lead to a reduction of the number of facets in the eye and duplications of the antennae and maxillary palpi (159). There is no definitive evidence that *Dfd* mutations cause homeotic transformations, but the mutant phenotype must be examined more closely. The molecular cloning of the ANT-C still has to be extended toward the centromere to include the *zerknüllt (zen), proboscipedia (pb),* and *labial (lab)* loci (71). There are at least two more homeoboxes that have been cloned on the basis of cross-homology and were mapped by in situ hybridization to this chromosome section (W. J. Gehring et al, unpublished results).

The Bithorax Complex

The genetic organization of the Bithorax complex has been studied in great detail (97–100), and the entire complex has been molecularly cloned by chromosomal walking (10, 11, 68). A DNA map indicating the location of some of the major mutations and transcripts is shown in Figure 1. The *Ultrabithorax (Ubx)* domain (Figure 1, section *b*) specifies the region from the posterior mesothorax (T2p) to the anterior first-abdominal segment (A1a), whereas the abdominal domain of the complex (Figure 1, part *c*) specifies the segments from posterior A1 to A8. Three lethal complementation groups have been identified, *Ubx, abdominal-A (abd-A),* and *Abdominal-B (Abd-B)* (131, 157), and correspond to three transcription units, each containing a homeobox. Molecular analysis (9, 54) indicates that the structural organization of the *Ubx* domain is unusually complex. The *Ubx* locus forms a large (~70-kb) transcription unit, extending from coordinates –31 to –104 kb.

Three types of *Ubx* transcripts have been identified. A major 3.2-kb *Ubx* transcript consists of four exons, including two internal microexons of 51 bp. The 5'-exon has two donor splice sites, one being 27 bp removed from the other. Alternative splicing at this site would lead to the formation of RNA's encoding two proteins differing by only nine amino acids, since the same open-reading frame downstream of the splice sites is maintained in both cases. The 3'-exon contains a homeobox. A 4.3-kb transcript extends further at the 3'-end, whereas the 4.7-kb RNA does not include the homeobox and is not polyadenylated. Chromosome breakpoints scattered along the entire 70 kb (3, 10) result in the *Ubx* phenotype (Table 1), which includes the transformation of four consecutive compartments (T2p through A1a).

The recessive *anterobithorax (abx)* and *bithorax (bx)* mutants, which are located within the *Ubx* transcription unit, transform only one or two compartments within the *Ubx* domain (see Table 1). They are thought to represent subfunctions of *Ubx*. It is not known whether these mutations affect unidentified transcripts within the *Ubx* unit that have different splicing patterns or whether they represent mutations in regulatory sites like "compartment-specific enhancers."

The *bithoraxoid (bxd)* transcription unit has some puzzling features (54). It is approximately 25-kb long (Figure 1, section *c*) and encodes a group of 1.2-kb RNAs that are expressed early in embryogenesis. These RNAs presumably share the 5' exon and the central exon, which are spliced to one of a group of five exons at the 3' end. Sequence information suggests that these early transcripts are not actually mRNA, since they contain no significant AUG-initiated open-reading frames within a 1144-bp sequence. This possibility suggests some regulatory role for these RNAs. Since there is significant

potential for base pairing between the introns of the *bxd* primary transcript and intronic sequences of the *Ubx* transcript, it was proposed that the two transcripts might interact during splicing (54), but no direct evidence supports this hypothesis. In addition, a late 0.8-kb polyA$^+$ *bxd* RNA is found in third-instar larvae, pupae, and adults. It appears to derive from a single exon near coordinate –14 (not shown in Figure 1). This transcript may encode a protein, as it contains a significant open-reading frame.

The abdominal region of the BX-C extends over approximately 175 kb of DNA in which a large number of mutations have been mapped (68; Figure 1, part *c*). A map of the corresponding transcripts is not yet available, but there is evidence that at least one transcription unit spans the *infra-abdominal-2 (iab-2)* region, and a homeobox is located near the 3' end, as in other homeobox-containing genes. The *iab-2* transcription unit corresponds to *abd-A* in the nomenclature of Sanchez-Herrero et al (131). These workers have recently proposed that the abdominal region of the BX-C contains only two complementation groups, *abd-A* and *Abd-B*. Mutations in *abd-A* would transform A2 through A4 into A1, and mutations in *Abd-B* would transform A5 through A8 into A4 (131, 157). However, their screen has failed to recover mutations such as *iab-4,5^{DB}*, which is homozygous viable, but completely sterile due to the lack of gonads. This mutation has a 28-kb deletion between *abd-A* and *Abd-B*. It seems that certain subfunctions can only be affected by specific deletions or insertions in the transcribed region (68). *Abd-B* presumably corresponds to *iab-7* and correlates with the presence of another homeobox (126). The complementation between the different *iab* genes is only partial and has been explained by cis interactions between the genes (68, 100). As in the *Ubx* domain, it is not clear whether there are different transcripts for each function or whether the cis-acting control regions contain segment-specific control elements.

Another possibly related gene, which, however, maps outside of the BX-C is the homeobox-containing gene *cad* (114). The *cad* gene is specifically expressed in the last abdominal segments (Figure 2). Since the deletion of the entire BX-C does not transform the most posterior abdominal segments, *cad* may specify the identity of these segments. Other than a large deletion, no mutants are known at the *cad* locus.

THE HOMEOBOX

The homeobox was discovered as a region of cross-homology between *Antp, ftz,* and *Ubx* (108, 109, 137). Cross-homologies between regions of different genes are fairly common, but the significance of the homeobox homology is highlighted by the fact that this small segment of DNA can be used as a probe to isolate other homeobox-containing genes. These genes are either homeotic,

as defined above, or are otherwise involved in determining the spatial organization of the embryo. Surprisingly, homeobox-containing genes are not confined to *Drosophila* and other arthropods. They have been found in higher animals, including mammals, and also in man (15, 95, 108–111, 119). More than 29 homeoboxes have been sequenced, 10 from *Drosophila* and at least 19 from other species. The homeobox is a highly conserved DNA segment of approximately 180 bp that is generally located in the exon nearest the 3' end of the genes in which it is found, close to the intron/exon boundary.

All 29 sequences share one common open-reading frame encoding a protein domain designated the "homeodomain." For the 10 Drosophila genes the homology ranges from 48% to 81% at the DNA level, and from 38% to 88% at the protein level. The 6 genes located in the ANT-C *(Antp, ftz, Scr, Dfd)* (84, 109, 126, 137) and the BX-C *(Ubx, iab-7)* (109, 126, 137) are more closely related to one another with respect to their homeobox sequences than the four genes located outside these gene clusters. Among the "outsiders" *engrailed (en)* and *engrailed related (er = invected, inv)* are closely linked and form a pair of closely related sequences (30, 125). The *cad* gene (114) and a newly discovered homeobox-containing gene at the 99B locus (B. Jacq, unpublished), however, differ considerably from all other sequences. The degree of homology is even more striking if one compares homeobox sequences from species as different as *Drosophila* and man. Homeoboxes in *Antp* and the human *C1* clone share 86% homology at the DNA level, and 98% at protein level, i.e. 59 out of 60 amino acids are identical (11a). Comparison of all 29 homeodomain sequences demonstrates that 12 out of 60 amino acids are invariant and are found in all 29 sequences. The most commonly found amino acid at a given position is always the one found in the *Antp* protein (with a single exception at position 6). This suggests that the *Antp* homeobox may be the ancestral or prototype sequence (W. J. Gehring, unpublished).

A first indication concerning the function of the homeodomain came from a computer search through protein data banks (139). A small but significant degree of homology was found between the homeodomain and the amino-terminal region of the proteins encoded by the yeast mating-type loci. This observation is of considerable importance, since the *MAT-α2* gene was shown to encode a sequence-specific DNA binding protein that regulates the transcription of a group of genes involved in mating-type differentiation and sporulation. More recently, some homology has been found between the homeodomain and another yeast protein that is encoded by the gene *ARD 1*, which is involved in the switch between alternative developmental pathways (171). Because there is also some homology between the MAT proteins of yeast and the prokaryotic gene-regulatory proteins (124) in the helix-turn-helix motif, which is involved in binding to the target DNA, these homologies suggest that the homeodomain may be a DNA binding domain (85, 139). The

homeodomain is about as large as the entire cro protein, a well-characterized regulatory protein of bacteriophage lambda, whose activity is mediated by its sequence-specific DNA binding properties (124). Immunolocalization studies indicate that the homeotic proteins of *Ubx* (9, 170), *ftz* (16), *en* (25), and *Antp* (J. Wirz et al, unpublished) accumulate in the nuclei, which is consistent with the hypothesis that they bind to DNA. Preliminary in vitro studies suggest that homeotic proteins bind specifically to DNA sequences located at the 5' ends of their target genes (24; P. A. Beachy, unpublished, H. Krause & J. Wirz, unpublished).

EVOLUTIONARY CONSIDERATIONS

Mutations exhibiting phenotypes similar to those of homeotic mutants in *Drosophila* have been found in various insects (35, 123). The best-known example is the *E* locus of the silkmoth *Bombyx mori*. Mutations in the *E* locus alter segment identity and have properties similar to those of the BX-C (63, 151). Using the homeobox as a probe, parts of the *E* locus have been cloned, indicating that this locus also contains homeobox sequences (Y. Suzuki, personal communication). Homeotic transformations have been found in many arthropods. Whether true homeotic mutations exist in vertebrates is an open question. Several candidates are being considered (53, 140, 155), but no definite evidence supports any of them at this time. It should be pointed out that the body plan of protostomes differs considerably from that of deuterostomes, and that the formation of the their body segments is basically different. However, the presence of the homeobox in vertebrates raises the possibility that homologous genes may be present, and the homeobox provides a tool to isolate such genes.

The first evidence for the presence of homeobox sequences in vertebrates came from whole-genome Southern blotting experiments (109), and subsequently the first homeoboxes from *Xenopus* (15), mouse (110), and man (95) were cloned and sequenced. An evolutionary survey based on whole-genome Southern blotting experiments, which detect homologies down to the 50% level, shows that the homeobox is present in animals that show segmentation, such as arthropods, annelids, and vertebrates. No homologous sequences were detected in some mollusks and nematodes (111), which lack overt segmentation. However, sea urchins, also lacking overt segmentation, have homeobox sequences (111) that were recently cloned and sequenced (26). Therefore, homeobox-containing genes may have a more general role in specifying the body plan.

The functional role of homeobox-containing genes in the mouse is unknown, but these genes are developmentally regulated (19, 20, 45, 48, 64, 66). There is also evidence for tissue-specific expression of homeobox-

containing genes in the mouse, and one gene that is specifically expressed in mouse testis has been isolated (D. Wohlgemuth, personal communication). The first in situ hybridization experiments indicate that two of the mouse genes that contain a homeobox are differentially expressed in the central nervous system (hindbrain and spinal cord), similar to *Antp* and *Ubx* (7). In order to discover whether the vertebrates have truly homeotic genes, we must also consider the protein sequences flanking the homeobox. It seems that genes homologous to the *en* gene have been found in the mouse (66) and the honeybee (U. Walldorf et al, in preparation). In comparing the sequences near the carboxy-terminus of the putative protein it is found that the homology between the proteins extends beyond the homeobox for another 20 or 30 amino acids. Sixteen out of 20 amino acids are identical between mouse and *Drosophila,* and 27 out of 30 are identical between the bee and *Drosophila.* If this homology also extends toward the amino-terminus of the protein, then we would have to conclude that the mouse possesses a bona fide *engrailed* gene, suggesting that the basic mechanisms controlling development are more similar in mammals and insects than had been anticipated.

EXPRESSION OF THE HOMEOTIC GENES

Molecular cloning of the homeotic genes makes it possible to study their spatial and temporal pattern of expression during development. The two major techniques used are the localization of homeotic gene transcripts by in situ hybridization, and detection of homeotic proteins using antibodies raised against polypeptides made in bacteria.

The expression pattern of homeotic genes is rather complex because it changes rapidly with time, and also because many homeotic genes produce multiple transcripts, which may have different spatial or temporal distributions. However, the most important aspect of the expression is that the homeotic selector genes are expressed in a segment-specific manner during embryogenesis and during larval development.

The expression patterns of six homeotic genes in the ANT-C and BX-C (i.e. *Dfd, Scr, Antp, Ubx, abd-A, Abd-B)* have a number of characteristics in common. We consider three stages of embryonic development for the description of the expression pattern (Figure 2). The first stage is the blastoderm, which is the earliest stage in which a definite spatial pattern can be observed. For all three genes examined so far *(Dfd, Antp,* and *Ubx)* the major site of expression is a region of one-to-two-segment width (Figure 2, part *a*) (5, 94, 108). Comparison with the embryonic fate map (46, 47, 104, 152, 158) suggests that these regions correspond to the primordia of the segments that are most severely affected by the mutations in those genes. In the second stage, germ-band extension, *Dfd, Antp,* and *Ubx* show more expanded pat-

terns of expression; the transcripts accumulate rather uniformly in a large region of the germ band (5, 44, 94, 106). From this stage on, mesodermal cells display a slightly different pattern. In the third stage, after the retraction of the germ band, the principal tissue of expression is the ventral nervous system. At this stage the major region of expression is again restricted to one-to-two-segment width (2, 5, 42, 44, 84, 94, 106, 108, 126). Immunofluorescent detection of *Ubx* and *Antp* protein reveals that the protein is localized in the nuclei of the cells expressing the corresponding RNA (9, 169, 170; J. Wirz et al, unpublished). The expression pattern is extremely fine grained, suggesting control either on a cell-by-cell level or according to cell lineage.

During the larval stages homeotic gene products are detected in cells of the imaginal discs in a segment-specific manner (2, 94, 169, 170). In the case of the *Antp* gene, the region of the wing imaginal disc expressing the $Antp^+$ mRNA and protein coincides precisely with the region transformed in $Antp^-$ mutants (94, 134; J. Wirz, unpublished). These expression patterns are consistent with the hypothesis that homeotic genes, such as *Ubx* and *Antp*, function as selector genes in establishing the identity of each segment.

Other homeobox-containing genes are also expressed in a spatially restricted manner. At the blastoderm stage RNA and protein products of the segmentation genes *ftz* and *en* accumulate in stripes with a periodicity corresponding to double and single segments, respectively (see Figure 2, part *a*) (16, 25, 30, 41, 81, 164). Both genes are also expressed in a segmental fashion in specific neuronal precursors of the ventral nervous system (16, 25, 52, 61). The *en* gene is also expressed in the posterior compartment of the imaginal discs (81). The *cad* gene is the only known homeobox-containing gene in *Drosophila* that is expressed maternally. Its transcripts form an anterior-posterior concentration gradient in preblastoderm embryos. By the blastoderm stage a single band of transcripts close to the posterior end of the embryo is detectable (114). Zygotic expression has been detected in the proctodaeum, the Malpighian tubules, and the posterior midgut of the embryos, as well as in the genital discs and the gonads of the larva in both sexes (M. Mlodzik & W. J. Gehring, unpublished).

REGULATION OF HOMEOTIC GENES

How the segment-specific spatial pattern of expression is achieved is one of the central questions relevant to the understanding of homeotic genes. There is some evidence suggesting that a common mechanism exists for controlling the expression of most, if not all, of the homeotic genes. First, there is a set of genes that appears to affect the expression of many homeotic genes simultaneously as judged from the mutant phenotype. Second, as discussed

above, similarities exist between the patterns of expression of different homeotic genes during development.

Transregulatory Genes

A number of mutations have been identified that cause homeotic transformations in such a way that all segments look alike (*esc:* 142; *Pc:* 22, 27; *Pcl:* 28; *Asc, Psc, Pcm:* 67; *trx:* 14, 55, 60; *sxc:* 57; *fs(1)h:* 31; *ph:* 29). Most mutations direct transformation toward A8, whereas one (*trx,* also called *Rg-bx)* causes transformation toward T2. In all cases studied, the phenotype of these mutations is dependent upon the presence of homeotic genes in the BX-C and the ANT-C, suggesting that they are involved in the selective expression of the homeotic genes (14, 28, 57, 67, 132, 133, 142, 146). Indeed, in the cases of *Pc, esc, sxc,* and *trx* it has been shown that mutations do alter the spatial distribution of the product of the *Ubx* gene and other homeotic genes (9, 12, 62, 149, 150, 162, 168).

How these transregulatory genes are involved in the expression of homeotic genes is not known. Many of the mutations show a maternal effect, suggesting that the product is synthesized and required during oogenesis (28, 50, 57, 142). However, developmental studies with *esc* indicate that the time of gene action is rather late, i.e. the temperature-sensitive period is around the onset of gastrulation, and the mutation does not affect the initial expression of the *Ubx* gene (145, 149). Furthermore, the *esc* phenotype can be repressed by the *trx* mutation (56). These results suggest that *esc* is not involved in initiation of the *Ubx* gene expression, but rather is required for stabilization of the proper pattern of expression. Recent cloning of some of the transregulatory genes (24a, 32; R. Paro & D. Hogness, personal communication) should give some insight into the mode of action of these genes. We also expect that promoter fusion experiments in which the promoter of a homeotic gene is fused to an indicator gene (like *lac*Z in *E. coli.*) will shed some light on the question of whether transregulatory control occurs at the transcriptional level or posttranscriptionally.

Cis-Acting Control Sequences

One way to elucidate the control mechanisms of gene expression is to identify cis-acting regulatory sequences and then to look for the regulatory factors that interact with them. In the case of the segmentation gene *ftz,* various morphogenetic control elements have been identified in the 5'-flanking region of the gene through the use of promoter fusion genes in which the *ftz* promoter is fused to the *lac*Z gene in *E. coli,* which encodes β-galactosidase. (52). A similar approach with the *Antp* gene reveals control elements responsible for segment-specific expression (S. Schneuwly et al, unpublished). On the other hand, some insights into the control sequences of the *Ubx* gene can be

obtained from the molecular nature of the *Ubx* subfunction mutants and dominant gain-of-function mutants, which show parasegment- and/or compartment-specific transformation. Studies with *Ubx* antibody indicate that the distribution of *Ubx*-encoded protein in these mutants is not simply increased or decreased, but show compartment-specific changes (12, 167, 168). Lesions in these mutants (transposon insertions or small deletions) are located in specific subregions of the *Ubx* gene, depending on their phenotype (9, 10). Since these mutations are located in DNA segments that are presumably noncoding, it is possible that regions disrupted by these mutations define regulatory elements responsible for the compartment- and/or parasegment-specific expression.

In the BX-C, mutations in one gene can "inactivate" a distal neighboring gene in cis (termed "cisvection") or "overexpress" the next proximal gene in the anterior segment (100). Synapsis-dependent complementation between certain mutations (38) appears to be at least partly due to this effect (100). Germ-line transformation experiments using cloned DNA segments should provide information concerning the significance of the physical organization of the homeotic gene complexes.

Interactions Among Homeotic Genes

Another class of genes involved in the regulation of homeotic genes is that of the homeotic genes themselves. Earlier genetic studies provided evidence suggesting that regulatory interactions occur among homeotic genes such that the activity of one gene represses that of another (144). Use of molecular probes to localize homeotic-gene products has permitted the visualization of such interactions in the embryo. For example, the *Antp* gene is expressed in a posterior region of the embryo when the T2 segment is reiterated by mutations in the BX-C (43). One interpretation of these data is that Ubx^+ and other genes in the BX-C are involved in repression of *Antp* expression. Similarly, *Ubx* appears to be regulated by the more posterior genes, i.e. the *abd-A* and the *Abd-B* genes (150, 168). However, BX-C mutations do not change the initial pattern of *Antp* expression in the blastoderm (44). Therefore, it is likely that the interaction occurs later, when expression of homeotic genes changes from a rather broad pattern at the germ-band-extension stage to a refined pattern after germ-band retraction.

What, then, controls the early pattern of expression of homeotic genes? First, we expect that maternal-effect genes, which are thought to be involved in establishing the coordinate system in the embryo (103, 122), are required for the correct spatial expression of homeotic genes. Second, some members of the class of segmentation genes (121) may be involved in this process, since certain mutant alleles of segmentation genes show a homeotic phenotype (71, 85, 93, 98a). All of the cloned segmentation genes are already

expressed at the blastoderm stage (41, 58, 69, 78, 79, 164). Protein products of the pair-rule genes *ftz* and *en* have a homeodomain (30, 83, 85, 108, 125). The protein encoded by a gap gene *(Kr)* has homology to *Xenopus* transcription-factor IIIA (128). These proteins may regulate homeotic gene expression by binding to DNA and/or RNA. Third, there are transcription units in the BX-C and ANT-C that contain only small open-reading frames (54; A. Kuroiwa et al, unpublished). Transcripts from *bxd* (in BX-C) and gene *X* (in ANT-C) are localized in a limited region of the blastoderm (6, 84). Since *bxd* mutations alter the distribution of *Ubx* protein, at least in late embryos (9, 168), it is possible that these RNAs serve a regulatory function. However, the precise function of these RNAs remains elusive.

MECHANISM OF ACTION

Segmentation in *Drosophila* and other insects is thought to result from the super-imposition of two patterns: the periodic pattern of segments and the sequential pattern of segmental identities. The two patterns are affected separately by mutations altering either the number and polarity of the segments (segmentation genes) or segmental identity (homeotic genes). For example, segmentation genes such as *paired* delete portions of alternate segments giving rise to an embryo with only half the number of segments (121). The identity of the remaining segments appears not to be affected, indicating that in this case the periodic pattern alone is altered. On the other hand, the deletion of the entire BX-C changes the identity of most segments without affecting segment number. Meinhardt proposed a model (112, 113) to explain the periodic pattern of segmentation on the basis of an overall anteroposterior gradient formed in the egg under the control of maternal genes, followed by the position-dependent interaction of the gradient early in embryogenesis with a hierarchy of segmentation genes, first the gap genes and later the pair-rule genes. Gap mutants delete one continuous stretch of segments, whereas pair-rule genes (e.g. *paired*) delete alternating portions of the periodic pattern (121). This model accounts for many experimental observations concerning the formation of the periodic pattern.

Lewis (99) has proposed a working model for the sequential pattern of segmental identities, which assumes that the different genes of the BX-C are active in different segments. Since deletion of the entire complex transforms all posterior segments from T3 through A8 into a segment resembling T2, the ground state in which the minimum number of BX-C genes has to be active is considered to be T2. One additional gene is expressed in each consecutive segment until segment A8, where all genes of the complex are presumably active. The model provides an explanation for the observation that loss-of-function mutants lead to anterior segmental transformations (Table 1), and it

is consistent with the observed effects of partial deletions of the complex. The model can also be extended to include the ANT-C (144, 146), although there are some difficulties with the notion of the ground state; the deletion of *Scr* appears to give both anterior and posterior transformations, i.e. toward and away from the ground state.

The recent molecular studies on the expression of homeotic genes give a somewhat different picture, which leads us to propose a modification of the Lewis model. In situ hybridization experiments with *ftz* show that the periodic segmental pattern, as reflected by the position-dependent expression of the ftz^+ gene (Figure 2), is generated even prior to completion of the blastoderm, followed by the further subdivision into anterior and posterior compartments, as indicated by the periodic pattern of *en* expression (30, 41, 81, 164). The homeotic genes are expressed in an anteroposterior order (Figure 2), with maximal expression in those segments they are thought to specify. During germ-band extension weak expression is also observed in all posterior segments, as predicted by the Lewis model, but during germ-band retraction the accumulation of both the transcripts and the respective proteins is largely confined to the segments they specify. These observations can be explained by assuming that the homeotic gene expressed more anteriorly is repressed in the more posterior segments by the next posterior gene. This interpretation is supported by the experiments described above, which demonstrated that an anterior gene becomes strongly expressed in consecutively more posterior segments if the next posterior gene is deleted (43, 150). Thus, *Antp* expression is prevented in the next posterior segments by *Ubx*, which in turn is repressed by *abd-A* (43, 150). Although this observation applies to the accumulation of both the mRNA and protein, there is no evidence yet that this interaction between homeotic genes is direct. However, preliminary in vitro DNA binding studies may suggest a direct interaction (P. A. Beachy, unpublished). The consecutive repression of the homeotic genes by the next posterior gene can also explain the anteroposterior sequence of segmental identities. Our model of sequential interaction between homeotic genes is consistent with the observed loss-of-function phenotypes that lead to the transformation of the respective segment into the next anterior one.

The mechanism of action of the dominant gain-of-function mutants has been an enigma for molecular biologists, since many of the mutants constitute complex chromosomal rearrangements. However, recent evidence shows that at least one class of such mutants that are caused by chromosomal inversions in the *Antp* gene lead to the fusion of the *Antp* protein–coding region to a foreign promoter (S. Schneuwly et al, unpublished). Using P factor–mediated germ-line transformation it was shown that the dominant gain-of-function phenotype can be induced by the overexpression of the normal *Antp* gene at ectopic sites (S. Schneuwly, R. Klemenz & W. J. Gehring, unpublished).

Similarly the dominant gain-of-function mutants *Cbx* and *Hm* lead to the ectopic expression of the *Ubx* gene (12, 167).

In order to explain the mechanism of action of homeotic genes in controlling segmental identity or developmental pathways, one must assume that these genes also interact with genes at the next lower level of the hierarchy of control and, directly or indirectly, with the structural genes that encode the products required for morphogenesis. The identification of these genes and the elucidation of the controlling circuits is a major task for the future.

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