Analysis

The *Drosophila melanogaster* Genome: Translation Factors and RNA Binding Proteins

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The *Drosophila melanogaster* genome includes ~300 genes encoding translation factors or proteins with well-characterized RNA binding motifs. Essentially all of the canonical eukaryotic translation factors were found among their predicted products. The four most numerous classes of RNA binding proteins are RNA recognition motif (RRM)[1] proteins, DEAD/DExH-box helicases, KH domain proteins, and double-stranded RNA binding domain (DSRBD) proteins. Many of these correspond readily to yeast or mammalian orthologs, and can therefore be predicted to have specific functions in pre-mRNA and pre-rRNA processing, translation initiation, and nuclear export of RNA. The genes encoding cytosolic translation factors, and those encoding each class of RNA binding protein, are discussed in turn below.

Translation Factors

Most genes encoding general translation factors that have been characterized in other species are present in the *Drosophila melanogaster* genome, and their products are similar to their mammalian counterparts (Table I). One possible exception is eIF4B, as the closest *Drosophila* homologue (CG10837) exhibits only modest BLAST similarity to the mammalian and yeast translation factor (1e-13 and 5e-03, respectively). Genes encoding several translation factors are present in two similar copies; these are eIF3-S4, eIF3-S5, eIF3-S7, eIF4A, eIF4H, eEF1α, and eEF2. Mutant alleles of a single eIF4A gene (CG9075) or of a single eEF1α gene (CG8280) are recessive lethal, indicating that, at least in these two cases, the related genes are not functionally redundant.

The *Drosophila* genome contains six genes encoding proteins highly similar to the mRNA cap-binding protein, eIF4E (Table I; Fig. 1). One of these, CG10716, is the probable ortholog of mammalian 4EHP (Rom et al., 1998). cDNAs have been identified for three of the genes encoding eIF4E-related proteins (CG8023, CG10124, and CG10716), indicating that at least these genes are expressed. I examined the five genes encoding proteins most closely related to eIF4E to determine the extent of conservation of eight residues critical in murine eIF4EI for binding the 7-methylguanosine cap (Marcotrigiano et al., 1997). All eight of these are invariant in the two alternative splicing products of the *Drosophila eIF4E* gene and in the five cognates (CG1442, CG8023, CG8277, CG10124, and CG11392), but not in mammalian 4EHP or CG10716. I also investigated whether the eIF4E cognates contained seven amino acids essential for eIF4G or 4EBP binding, and whether they possessed a serine residue that can be phosphorylated (Ser-251 in *Drosophila* eIF4EI), and a lysine residue (Lys-201 in *Drosophila* eIF4EI) with which P-Ser-251 is predicted to form a salt bridge (Marcotrigiano et al., 1999; Pyronnet et al., 1999). Another translation initiation factor, eIF4G, competes with an inhibitor protein, 4EBP, for the same binding site on eIF4E. Of the residues required for eIF4G or 4EBP binding, only CG1442 possesses all seven. CG8277, CG10124, and CG11392 all have a single conservative substitution among these seven residues, whereas CG1442 diverges at two residues. This analysis suggests that the eIF4E cognates all can bind 7-methylguanosine caps, but may interact with eIF4G and the inhibitor protein 4EBP in different ways, perhaps adding complexity to the regulation of cap-dependent translation. Ser-251 and Lys-201 are retained in CG8277, CG10124, and CG11392, but not in the other two, again suggesting differential regulation.

In the *Caenorhabditis elegans* genome, there are three eIF4E cognates in addition to a 4EHP ortholog (Keiper et al., 2000). Like the fly cognates, the nematode cognates all are invariant in the eight residues essential for 7-methylguanosine cap binding, but are somewhat variable in the eIF4G-interacting and phosphorylation residues. Whereas the *C. elegans* cognates have been implicated in binding the unusual trimethylated cap structure found in SL1 trans-spliced mRNAs, our results indicate that a diversity of eIF4E-like proteins exists in an organism which does not produce mRNAs with trimethylguanosine caps. In contrast to eIF4E, and unlike mammals (which have at least three), the *Drosophila* genome contains only a single gene encoding a recognizable ortholog of 4EBP.

RNA Binding Proteins

I analyzed >200 genes encoding proteins of the RRM, DEAD/DExH-box, KH domain, and DSRBD classes. These structural motifs are not absolutely predictive for an

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[1]*Abbreviations used in this paper:* DSRBD, double-stranded RNA binding domain; RBD, RNA binding domain; RRM, RNA recognition motif; Tat-SF1, Tat stimulatory factor-1.

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Table I. Drosophila melanogaster Genes Encoding Cytosolic Translation Factors

Translation factor	*Drosophila* gene	BLASTP value to mammalian homologue
eIF1A*	CG8053	9e-42
eIF2α*	CG9946	1e-85
eIF2β*	CG4153	8e-76
eIF2γ*	CG6476	0.0
eIF2B-α	CG7883	4e-75
eIF2B-β	CG2677	5e-85
eIF2B-γ	CG8190	9e-70
eIF2B-δ	CG10315	1e-93
eIF2B-ϵ	CG3806	1e-79
eIF3-S1	CG12131	7e-21
eIF3-S2*	CG8882	e-118
eIF3-S3	CG9124	9e-65
eIF3-S4	CG10881	1e-61
	CG8636	6e-59
eIF3-S5	CG9769	1e-73
	CG8335	1e-46
eIF3-S6	CG9677	e-151
eIF3-S7	CG10161	e-173
	CG4810	e-157
eIF3-S8	CG4954	0.0
eIF3-S9	CG4878	0.0
eIF3-S10	CG9805	0.0
eIF4A*	CG9075	e-163
	CG7483	e-149
eIF4B (?)	CG10837	1e-13
eIF4E*	CG4035	7e-56
	CG10124	4e-50
	CG11392	5e-50
	CG8277	9e-46
	CG1442	3e-35
(4EHP)	CG10716	5e-18
	CG8023	8e-04
eIF4G*	CG10811	3e-29
eIF4H	CG4429	7e-23
	CG1340	2e-20
eIF5	CG9177	e-105
eIF5B* (dIF2)	CG10840	e-156
eIF6	CG17611	e-110
eEF1α*	CG8280	0.0
	CG1873	0.0
eEF1β*	CG6341	3e-56
eEF1γ	CG11901	e-134
eEF1δ	CG4912	2e-54
eEF2*	CG2238	0.0
	CG4849	e-174
eRF1	CG5605	0.0
eRF3*	CG6382	e-127 (yeast)

Because of space constraints, other genes encoding mitochondrial translation factors are excluded. BLAST probability scores were derived using BLASTP against the nonredundant protein database at ncbi.nlm.nih.gov/BLAST.
*Indicates genes that had been cloned and sequenced before the genome sequencing effort.

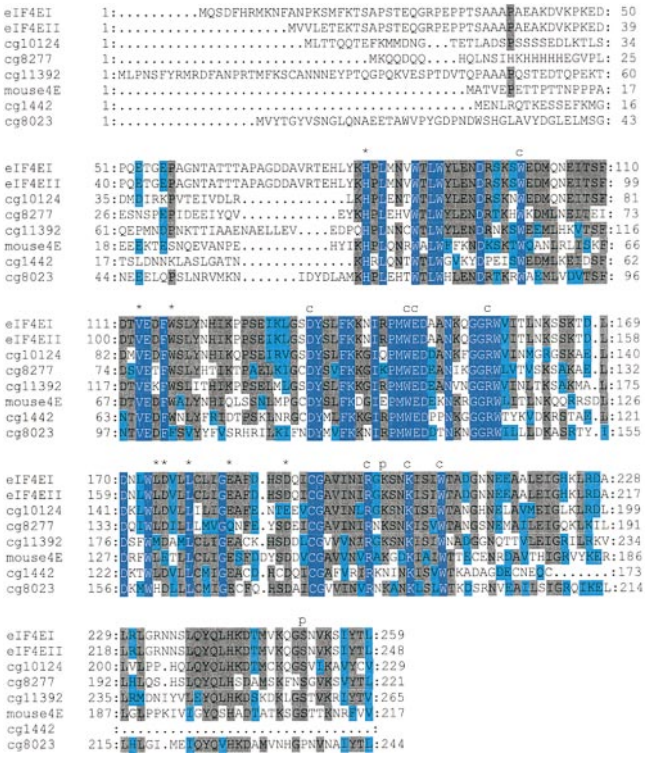

Figure 1. Sequence alignment of two *Drosophila* eIF4E isoforms produced by alternative splicing from the *eIF4E* gene (eIF4EI and eIF4EII; Lavoie et al., 1996), *Mus musculus* eIF4E (mouse4E), and five novel *Drosophila* genes that encode related proteins. Residues identical in all eight proteins are printed white with black background, other well-conserved residues are printed with shaded background. Each residue essential for cap binding is marked with a lower case c, each residue essential for binding to eIF4G or 4EBP is marked with an asterisk, and each residue involved in phosphorylation is marked with a lower case p. The alignment was produced using CLUSTALW (Thompson et al., 1994).

RNA binding function, particularly as for several DExH-box helicases experimental evidence indicates a function in DNA, rather than, or in addition to, RNA binding. Overlap between DNA and RNA binding functions is also evident from recent work on the *Drosophila* homeodomain-containing protein, Bicoid, which was found to bind and regulate translation of *caudal* mRNA. Bicoid, like other homeodomain-containing proteins, has a well-established function in DNA binding and transcriptional regulation. The RNA binding function of Bicoid is not mediated by its homeodomain but, surprisingly by a PEST motif (Niessing et al., 1999), which is usually associated with protein degradation. It is possible that further experimental work will prove that dual functionality of proteins, and unexpected functions for conserved motifs, are relatively common. Conversely, the *Drosophila* genome contains an unknown number of other RNA binding proteins, not listed here, that lack the canonical domains that allow such a function to be predicted. Apontic (Lie and Macdonald, 1999) is an example of such a protein, for which experimental evidence of an RNA binding function has been obtained despite the absence of known RNA binding domains (RBDs). Similarly, no zinc finger proteins are included here, although some C_2H_2 zinc finger proteins bind RNA. It is not possible using presently available algorithms to predict an RNA binding function rather than a DNA binding function for a zinc finger protein based on sequence comparison.

RNA Recognition Motif Proteins

The *Drosophila* genome encodes 117 different RRM con-

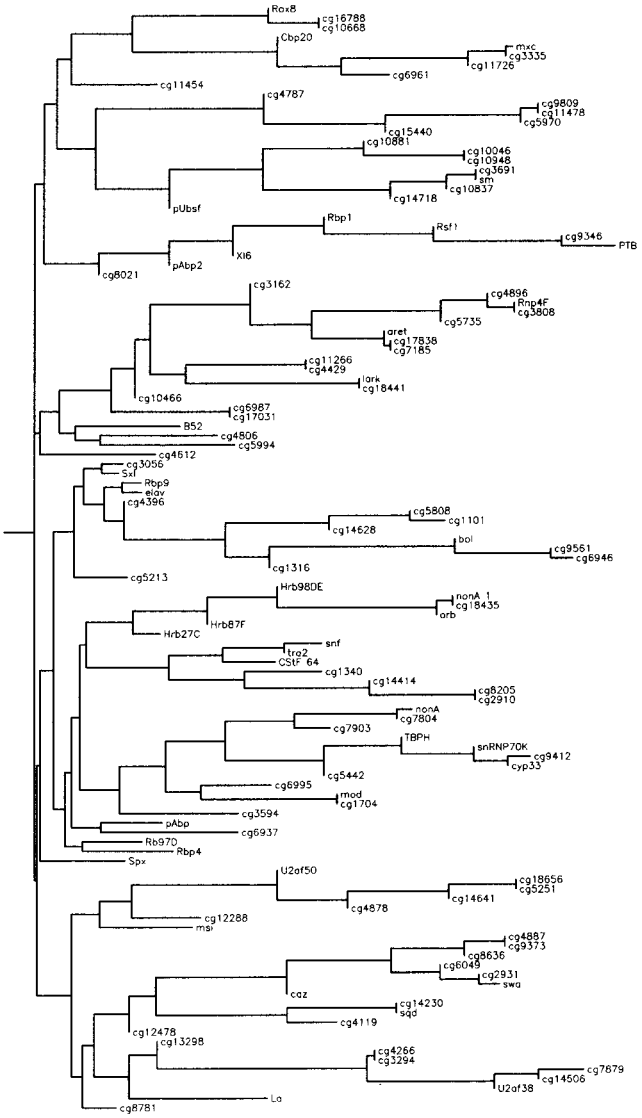

Figure 2. Phenogram of 117 *Drosophila* RRM proteins. The alignment was produced using CLUSTALW (Thompson et al., 1994) and the tree was generated using the protdist, neighbor, and drawgram programs in the PHYLIP package (Felsenstein, 1989).

taining proteins, rendering this type the largest class of RNA binding proteins. Fig. 2 presents a phylogenetic tree showing the relationships among these proteins. The RRM contains the shorter RNP-1 and RBD domains (Birney et al., 1993); in some RRM proteins, one or both of these shorter domains are the only ones easily recognized. However, the RNP-1 domain alone is not always predictive of an RNA-binding function, as it is present in several proteins that clearly have a different function, for example, Pk34A, a protein kinase, and laminin A, a cell adhesion molecule. In comparison to the RNP-1 motif, the RBD domain is more closely associated with an RNA binding function. Proteins with only an RNP-1 or RBD domain were used in BLASTP searches against the *Drosophila* genome, and were only included in Fig. 2 if several RRM proteins were recovered among the hits ($P < 0.01$). Many RNP-1 containing proteins, but only two RBD proteins (CG6997 and CG8919) were excluded from Fig. 2 by this process.

Of the RRM proteins encoded by the *Drosophila* genome, 74 have not been described previously. Particularly interesting among these are CG6049, which encodes a protein highly similar (BLASTP < 1e-80) to human Tat stimulatory factor-1 (Tat-SF1; Zhou and Sharp, 1996). Tat increases HIV-1 transcription at the level of elongation by binding to TAR, which forms a stem-loop structure at the 5′ end of the nascent viral transcript. Tat-SF1 is a cofactor for Tat, and has more recently been identified as a general transcription elongation factor (Li and Green, 1998). CG5251 encodes a probable ortholog (BLASTP < e-102) of human NOT4, a likely negative regulator of transcription (Albert et al., 2000). CG4887 is highly related (BLASTP < 7e-72) to LUCA15, a putative tumor suppressor gene in humans (Drabkin et al., 1999). CG4787 is very similar (BLASTP < 2e-40) to human TIA-1, an RNA binding protein that acts downstream of eIF2α phosphorylation in the assembly of mammalian stress granules, in which untranslated mRNAs accumulate during translation arrest consequent to environmental stress (Kedersha et al., 1999). Other RRM proteins involved in RNA processing are discussed in an accompanying review (Mount and Salz, 2000, this issue).

DEAD/DExH-box Putative Helicases

63 putative nucleic acid helicases of the DEAD, DEAH, and DExH families have been grouped into a phylogenetic tree (Fig. 3). Many of these proteins are extremely similar to yeast and mammalian counterparts. Numerous yeast helicases have been implicated in processing of pre-mRNAs or pre-rRNAs, in RNA export, or in the cases of TIF1/2 (eIF4A) and DED1, in translation initiation. A subset of DExH-box proteins function as DNA helicases, having roles in DNA replication and repair. The striking degree of conservation between individual yeast and *Drosophila* helicases often allowed a one-to-one correspondence to be drawn (see also Mount and Salz, 2000, this issue); in these cases, the name of the yeast ortholog has been added in parentheses to Fig. 2. This led to the assignment of probable functions to many of the *Drosophila* helicase proteins. CG9748 as a DED1 ortholog is likely to be involved in translation initiation, and is close phylogenetically to Vasa, which has been implicated experimentally in the same process (Carrera et al., 2000). The *Xenopus* ortholog of CG9748, An3, encodes an mRNA that is asymmetrically localized to the animal pole of the oocyte (Gururajan et al., 1991). Both An3 and DED1 have been implicated in export of RNPs from the nucleus. An3 protein binds to and is exported from the nucleus by the CRM1 nuclear export receptor (Askjaer et al., 2000), and in yeast DED1 genetically interacts with SRM1, which encodes the Ran-associated guanine nucleotide exchange factor, which in turn binds CRM1 (Hayashi et al., 1996; Taura et al., 1998). These data suggest a similar role in *Drosophila* for CG9748.

Comparison of the yeast and *Drosophila* helicase-encoding genes allowed many of the latter to be assigned functions in preribosomal RNA processing based on yeast

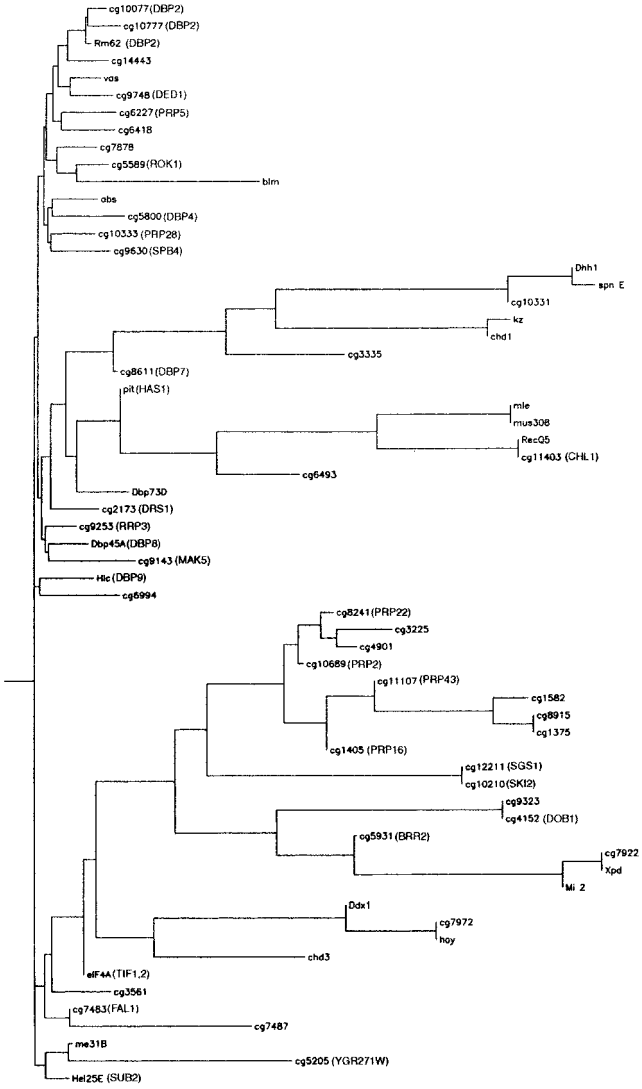

Figure 3. Phenogram of 63 *Drosophila* DEAD/DExH-box putative helicases, computed as in Fig. 2. Probable yeast orthologs are added next to the gene names in parentheses.

orthologs. These are: CG2173 (DRS1; Ripmaster et al., 1992); CG5589 (ROK1; Venema et al., 1997); CG5800 (DBP4; Liang et al., 1996); CG7843 (FAL1; Kressler et al., 1997); CG8611 (DBP7; Daugeron and Linder, 1998); CG9253 (RRP3; O'Day et al., 1996); and CG9630 (SPB4; de la Cruz et al., 1998). Similarly, CG4152 is implicated in mRNA export based on its yeast ortholog (DOB1; Liang et al., 1996). Several other *Drosophila* helicases can be assigned functions in pre-mRNA processing using similar reasoning (Mount and Salz, 2000; Fig. 3). Finally, CG11403 encodes an ortholog of yeast CHL1, a DNA helicase involved in chromosome transmission and progression through the G2/M cell cycle transition (Gerring et al., 1990).

KH Domain Proteins

The *held-out wings* (*how*) gene encodes a 382-amino acid protein with a single KH domain at its COOH terminus. *how* is essential for tendon cell differentiation, and a nuclear isoform of the How protein has been shown to bind a specific mRNA (*stripe*) and prevent its export (Nabel-Rosen et al., 1999). *how* is related to the murine *quaking* gene, which is required for Schwann cells to mature into myelin-forming cells in the peripheral nervous system (Ebersole et al., 1996). The *Drosophila* genome encodes a total of ten proteins highly related to *quaking*. Four of these (*qkr58E-1*, *qkr58E-2*, *qkr58E-3*, and CG10384; Di Fruscio et al., 1998; Fyrberg et al., 1998) are tightly linked in a gene cluster in cytological region 58E, and two others are nearby in 58F (CG3875) and 58A (CG4021). The final four members of this gene family (*how*, *Sam50*, CG9337, and CG18078) are unlinked.

A phylogenetic tree illustrating relationships among the 27 KH domain proteins predicted from the *Drosophila* genome is presented in Fig. 4. 18 of the 27 proteins possess only a single KH domain, but the others have multiple copies, as many as 13 (*Dp1*). One of the single KH-domain proteins (CG7878) also has a DEAD-box helicase domain. CG1691 encodes a product very similar (BLASTP $<$ 8e-88) to zipcode binding protein (ZBP-1), a protein with

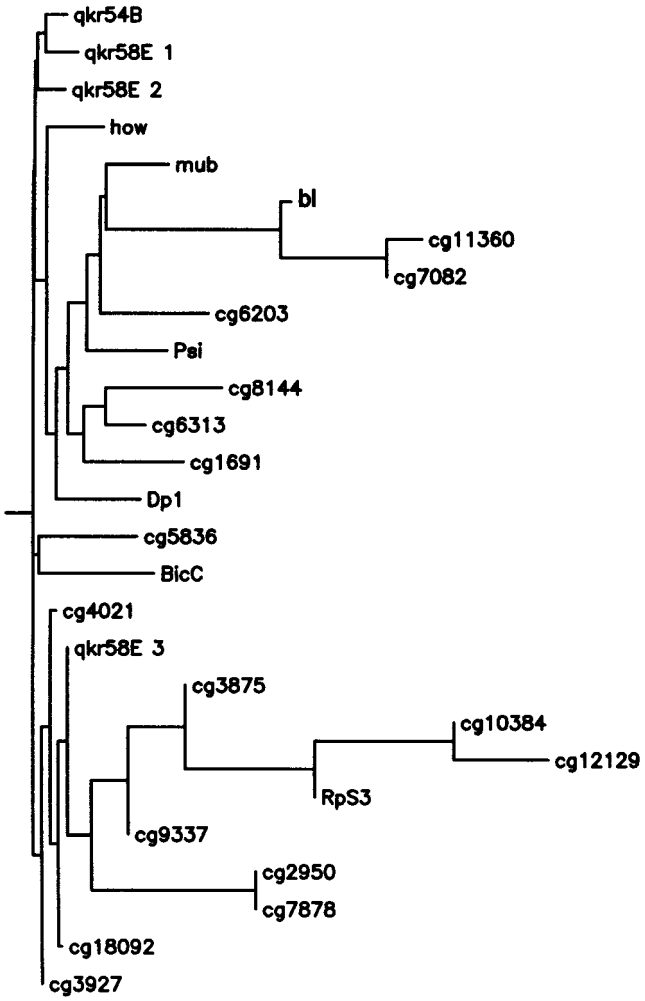

Figure 4. Phenogram of 27 *Drosophila* KH-domain proteins, computed as in Fig. 2.

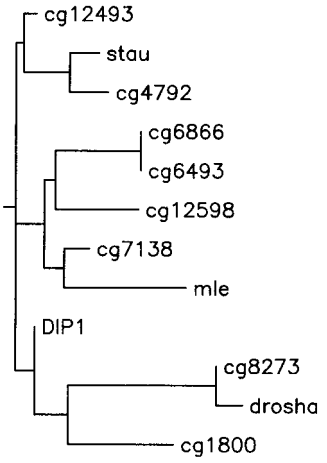

Figure 5. Phenogram of 12 *Drosophila* DSRBD proteins, computed as in Fig. 2.

four KH domains that binds to a specific site on β-actin mRNA and mediates its localization to the leading edge of chick embryo fibroblasts (Ross et al., 1997). A similar protein in *Xenopus*, Vera, is involved in localization of Vg1 mRNA to the vegetal pole of the oocyte (Deshler et al., 1998; Havin et al., 1998). This is of interest because, whereas asymmetric localization of specific mRNAs has been extensively studied in *Drosophila* oocytes, no ZBP-1 counterpart had previously been identified in flies. In addition to the four KH domains, ZBP-1 and Vera contain a single RRM; this is apparently absent from CG1691.

DSRBD Proteins

A phylogenetic tree illustrating relationships among the 12 DSRBD proteins predicted from the *Drosophila* genome is presented in Fig. 5. Two new genes for which possible functions can be assigned are CG6866, which encodes a protein highly similar (BLASTP < 2e-36) to the human TAR RNA binding protein, and CG12598, which encodes a putative deaminase involved in RNA editing (BLASTP < 7e-53 to human homologue). Mice bearing a targeted disruption of the CG6866 homologue (*Tarbp2*) are male-sterile, and the protein product of this gene, Prbp, has been proposed to have a role in the assembly of translationally regulated RNPs (Zhong et al., 1999).

Homologues of RNA Binding Proteins Implicated in Human Disease

Among the genes encoding KH-domain proteins, CG6203 encodes an excellent homologue (BLASTP < 6e-81) of the human fragile-X associated protein (FMRP; Ashley et al., 1993). Fragile X syndrome is the most common inherited mental retardation disorder in humans (Ashley and Warren, 1995). FMRP is believed to shuttle between the nucleus and the cytoplasm, and is associated with large mRNP complexes and ribosomes (Feng, et al., 1997; Ceman et al., 1999). CG8144 encodes a KH-domain protein highly similar (BLASTP < 6e-63) to the human paraneoplastic antigen Nova-2, an RNA binding protein implicated in paraneoplastic opsoclonus-myoclonus ataxia (POMA), a neurologic disorder with associated dementia (Yang et al., 1998). The structure of a KH domain from Nova-2 has recently been determined by X-ray crystallographic methods, and the domain has also been shown to be a sequence-specific RNA binding protein (Lewis et al., 2000).

Three DNA helicases included in Fig. 2 are homologues of genes implicated in human disorders: *bloom* (Bloom's syndrome; Kusano et al., 1999); *haywire* (xeroderma pigmentosum-B; Mounkes et al., 1992); and *Xpd* (xeroderma pigmentosum-D; Reynaud et al., 1999).

Concluding Remarks

The importance of posttranscriptional mechanisms of gene regulation, particularly at the level of translational control, is becoming increasingly apparent. Research in *Drosophila* has already provided many key insights into this field. Now that dozens of novel RNA binding proteins have been identified in the *Drosophila* genome, it is likely that our level of understanding of translational control will increase dramatically in the months and years to come.

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