DROSOPHILA, THE GOLDEN BUG, EMERGES AS A TOOL FOR HUMAN GENETICS

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Abstract | *Drosophila melanogaster* is emerging as one of the most effective tools for analyzing the function of human disease genes, including those responsible for developmental and neurological disorders, cancer, cardiovascular disease, metabolic and storage diseases, and genes required for the function of the visual, auditory and immune systems. Flies have several experimental advantages, including their rapid life cycle and the large numbers of individuals that can be generated, which make them ideal for sophisticated genetic screens, and in future should aid the analysis of complex multigenic disorders. The general principles by which *D. melanogaster* can be used to understand human disease, together with several specific examples, are considered in this review.

E-VALUES
The likelihood that an observed match between two gene sequences would arise by chance, given the sizes of the databases used for comparison.

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At the turn of the twentieth century, Thomas H. Morgan identified the *white* eye-pigment mutation. Since then, studies on *Drosophila melanogaster* have led the way in elucidating many basic biological processes. Morgan and his talented entourage, including Allan Sturtevant, Calvin Bridges and Hermann Muller, created the first genetic maps based on recombination frequencies, proposed the chromosomal theory of heredity and showed that X-rays induce mutations. As molecular biological tools became available in the 1970s and 1980s, *D. melanogaster* played a crucial part in defining how genes function in time and space to control development. A remarkable finding of these latter studies was that many genes involved in establishing the primary body axes, cell types and organ systems have been highly conserved during evolution. Now, a century after the initial studies of Morgan, and with complete gene sequences for many organisms in hand, the 'golden bug' is poised once again to address important genetic questions, this time at the whole-genome scale.

In this review, I concentrate on how *D. melanogaster* can be used as a tool to answer questions about the function of genes involved in human disease. I start by reviewing the various human disease genes with identified homologues in *D. melanogaster* and then focus on three areas in which *D. melanogaster* has already made significant contributions to the understanding of human disease processes, namely developmental disorders, neurological disorders and cancer. Finally, I consider some areas in which I believe *D. melanogaster* will have an important role in the future of human genetics.

Analysing human disease genes

***Drosophila melanogaster* homologues of human disease genes.** Given the high degree of evolutionary conservation among genes that control basic developmental processes, the availability of genome sequences of human and model organisms has provided a good opportunity to investigate the conservation of genes responsible for heritable diseases in humans. An initial answer was provided by conducting a comprehensive cross-genomic analysis: all human disease genes known to have at least one mutant allele listed in the Online Mendelian Inheritance in Man (OMIM; see Online links box) database were checked against the complete *D. melanogaster* genome sequence. This analysis, based on a regularly updated and interactive cross-genomic database called Homophila (see Online links box)[1,2], revealed several interesting facts that confirmed and extended previous

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METAZOAN
(pl. metazoa) A multicellular organism.

CELL AUTONOMOUS (FUNCTION)
If a gene's activity affects only those cells that express it, its function is cell autonomous; if it affects cells other than (or in addition to) those expressing it, its function is cell non-autonomous.

SECOND-SITE MODIFIER SCREENS
Genetic screens designed to isolate dominant mutations, which are carried out in organisms that are already genetically compromised for a given pathway or process. Such mutations would typically be recessive if generated in a wild-type background, but because the process of interest has been selectively weakened, mutations affecting other components in the pathway now become dominant, making the mutations much easier to identify.

INCLUSION BODIES
Nuclear or cytoplasmic aggregates found in the brains of patients affected by triplet-repeat diseases.

surveys of *D. melanogaster* disease genes[3,4]. First, 75% of all human disease genes have related sequences in *D. melanogaster* (defined by matches with expectation values (E-VALUES) $\leq 10^{-10}$); in fact, nearly a third of all human disease genes still have matches in the *D. melanogaster* genome when the scoring stringency is increased to a level that is typical of genes known to have functionally equivalent counterparts (for example, e-values $<10^{-100}$). On the basis of the current list of 2,309 human disease-gene entries, ~700 human disease genes are estimated to have sufficiently well-conserved homologues to be analysed in *D. melanogaster*. Second, *D. melanogaster* has homologues of genes that, when disrupted, cause a broad spectrum of human diseases such as neurological disorders, cancer, developmental disorders, metabolic and storage disorders and cardiovascular disease, as well as homologues of genes required for the visual, auditory, and immune systems. This and other bioinformatic analyses indicate that *D. melanogaster* can serve as a complex multicellular assay system for analysing the function of a wide array of gene functions involved in human disease (BOX 1).

As a high percentage of human disease genes have counterparts in *D. melanogaster*, several genetic disorders are currently being studied in flies. Representative examples of such studies are listed in TABLE 1 and online supplementary information S1 (table). These examples also span a broad range of diseases, from developmental disorders such as blindness, deafness, skeletal malformations and neural pathfinding disorders, to neurodegenerative diseases, mental retardation[5], cancer, cardiac disease and immunological disorders.

Box 1 | Advantages of *Drosophila melanogaster* as a model organism

Many of the genetic pathways that guide basic developmental processes in vertebrates and invertebrates have remained largely intact during evolution. This has greatly accelerated the analysis of vertebrate development, as insights gained from model genetic systems such as *Drosophila melanogaster* could be applied immediately to vertebrate systems. These studies have revealed that similar developmental mechanisms act throughout bilaterally symmetric METAZOA to accomplish several important processes that include: specifying segment identity along the anterior–posterior axis; subdividing the ectoderm into neural versus non-neural domains along the dorsal–ventral axis; defining the primary axes of appendage outgrowth from the body wall, organizing the formation of complex structures such as the eyes, the heart, the lungs and the innate immune system; guiding the initial outgrowth of axons with respect to the midline of the nervous system; and, potentially, controlling basic behaviours such as sleep or substance abuse (reviewed in REF. 6). In many cases, genes from one organism (for example, *D. melanogaster*) can functionally replace their counterparts in another organism (for example, a vertebrate).

On the basis of conservation of these genetic 'skeletons', it has been possible to reconstruct an image of the most recent common ancestor of bilateral animals; this organism resembles a primitive shrimp with six to eight segments, a well-defined nervous system and musculature, appendages and light-detecting organs. *Drosophila melanogaster* therefore serves as an excellent intermediate model system that fills a niche between unicellular organisms such as yeast and the slime mould *Dictyostelium discoideum*, which are ideal for studying CELL AUTONOMOUS eukaryotic functions such as DNA repair or cell division, and vertebrate systems such as mice or zebrafish, which can be used as accurate models for the human disease process. Therefore, diseases involving interactions between cells such as those affecting the formation or function of organ systems are ideally suited for analysis in *D. melanogaster*.

Experimental approaches. Of the many ways in which *D. melanogaster* can be used as a tool in these studies, the most common is to generate mutant lines of flies that model some aspect of the human disease. For example, as described in more detail below, either mutant fly or human triplet-repeat genes can be expressed in the fly eye to induce the degeneration of retinal photoreceptor cells. In these studies, proteins with wild-type numbers of triplet repeats have little or no effect when expressed in the eye, whereas those with longer repeats, which are associated with neurological disease states, cause degeneration and do so with a severity that increases with repeat number. These fly disease models can be used to study the cell-biological basis for the degeneration phenotype and are also a starting point for developing SECOND-SITE MODIFER SCREENS. Second-site modifier screens are fundamental to fly genetics as they can be used to identify genes that function in pathways common with the initially identified gene of interest. The typical final output of such screens is a list of 10–20 different loci, each with several independently generated alleles that either enhance or suppress the starting mutant phenotype (for example, partial retinal degeneration). The function of these genes in the process of interest (for example, the formation or clearing of intracellular INCLUSION BODIES) can then be analysed. One can also ask whether the human homologues of such genes map to genomic intervals associated with similar genetic disorders. As discussed below, this approach for identifying new human disease loci has been quite successful in the case of tumour-suppressor genes.

Drosophila melanogaster can also be used to address specific questions in human genetics that have been difficult to resolve using mouse knockout mutants or vertebrate cell culture systems. Such situations are relatively common given the greater genetic redundancy in vertebrates than in flies. In these approaches, which we have referred to as 'closing-the-loop' analyses[6], the goal is to rely on the conservation of genetic pathways or protein–protein interactions that underlie the function of a disease gene of interest, and then to design a genetic scheme to answer the particular question at hand. Examples of such closing-the-loop goals are summarized briefly in the last section of this review and include problems such as placing a novel disease gene that lacks sequence similarity to known genes in a genetic pathway; identifying human modifier loci, candidate protein targets of a disease gene or new candidate disease genes; and dissecting COMPLEX GENETIC TRAITS. For closing-the-loop analysis, it is important that hypotheses arising from the analysis in *D. melanogaster* are subject to well-defined tests in humans or a vertebrate disease model. It is not always necessary, however, to create a model that recapitulates specific aspects of the human disease in *D. melanogaster* so long as the relevant molecular interactions in flies and humans have been conserved. For example, one can identify genes that act in concert with the Notch receptor to generate the margin of the *D. melanogaster* wing and ask whether any of these genes are involved in entirely different Notch-mediated processes in vertebrates, such as skeletal formation.

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Table 1 | **Categories of human disease genes well suited to analysis in *Drosophila melanogaster****

Disease	Human gene symbol	Fly gene symbol	Gene product	References
Dysmorphology				
Synpolydactyly	*HOXD13*‡	*Abd-B*§	Transcription factor	140–142
Single bone in zeugopod	*HOXD3–HOXD13* (heterozygous deletion)	*Abd-B*§	Transcription factor	143,144
Hand-foot-genital syndrome	*HOXA13* or heterozygous *HOXA11–13* deletion	*Abd-B*§	Transcription factor	145–149
Aniridia	*PAX6*	*ey*§, *toy*§	Transcription factor	150–153
Townes-Brocks syndrome	*SALL1*	*salm*§, *salr*§	Transcription factor	154–156
Saethre-Chotzen syndrome	*TWIST1*	*twi*§	Transcription factor	133
Pfieffer syndrome	*FGFR1*, *FGFR2*	*htl*§	RTK	157
Apert syndrome	*FGFR2*	*htl*§	RTK	157
Crouzon syndrome	*FGFR3*	*htl*§	RTK	157
Saethre-Chotzen syndrome-like	*FGFR3*, gain-of-function?	*htl*§	RTK	133
Alagille syndrome	*JAG1*	*Ser*§, *Dl*§	Notch ligand	158
Spondylocostal dysostosis	*DLL3*	*Dl*§	Notch ligand	159
Primary congenital glaucoma	*CYP1B1*	*Cyp18a1*§	Cytochrome P450	108,109
Cardiac disease				
Congenital heart disease	*NKX2-5* *GATA4*	*tin*§ *pnr*§	Transcription factor Transcription factor	160–163 163–165
Holt–Oram syndrome	*TBX5*	*Doc1–Doc3*§	Transcription factor	166–168
DiGeorge syndrome	*TBX1*	*org-1*§, bi§	Transcription factor	169
Venous malformations	*TEK*	*htl*§	RTK	170
Neurological				
Spinocerabellar ataxia	*SCA1* (also known as *ATXN1*) *SCA2* (also known as *ATXN2*) *SCA6* (also known as *CACNA1A*) *SCA14* (also known as *PRKCG*) *SCA17* (also known as *TBP*)	*CG4547* *CG5166* *cac*§, *Ca-α1D*§ *inaC*§, *Pkc53E* *Tbp*§	Transcription cofactor? Unknown Ca^{2+} ion channel Ca^{2+}-dependent PKC TATA binding protein	27,30,171
Huntington disease	*HD*	*huntingtin*§	Axonal transport?	30,172–174
Spinal and bulbar muscular atrophy 3	*AR*	*ERR*, *svp*§	Androgen receptor	27,171
Parkinson disease	*PARK2* *PARK5* (also known as *UCHL1*) *PARK7* *NR4A2* *MAPT* *PINK1* *SNCA*	*park*§ *Uch* *dj-iβ*, *CG6646* *Hr38*§ *tau*§ *CG4523*§ None known	E3-ubiquitin ligase Ubiquitin pathway Androgen-R regulator? Nuclear hormone receptor Microtubule binding PTEN-induced kinase Dopamine transmission?	49–51 28–30 30,175 176 28–30
Alzheimer disease	*PSEN1*, *PSEN2* *APP*	*Psn*§ *Appl*§	γ-Secretase Signalling, axonal transport?	27–30,66
Fragile X syndrome	*FMR1*	*Fmr1*§	Translational regulator	72,177,178
Angelman syndrome	*UBE3A*	*dube3A*§	E3-ubiquitin ligase	179,180
Cancer				
Tuberous sclerosis	*TSC1*, *TSC2*	*tsc1*§, *tsc2*§	GAP for RHEB in TOR pathway	86,181–184
Endometrial carcinoma	*PTEN*	*Pten*§	Negative regulator PI3K	86,92
No known disease mutations in homologue	*LATS1*	*wts*§ (also known as *lats*)	Cyclin regulation?	94,95
Renal cancer lines	*SAV1*	*sav*§	Cyclin regulation?	96
No known disease mutations in homologue	*MST1*, *MST2* (also known as *STK3*)	*hpo*§	Cyclin regulation?	97
Bladder and colorectal cancer	RAS family genes	*Ras85D*§	RTK signalling	185
No known disease mutations in homologues	*SCRIB*, *LLGL1*, *DLG1*	*scrib*§, *l(2)gl*§, *dlg1*§	Cell polarity, metastasis in the presence of RAS-V12	
B-cell leukaemia	*CCND1*	*CycD*§	Cell cycle	93
Melanoma	*CDK4*	*Cdk4*§	Cell cycle	
Retinoblastoma	*RB1*	*Rbf*§, *Rbf2*	Cell cycle	
Hepatocellular carcinoma	*TP53*	*hth*§ ($e<10^{-10}$)	Cell cycle	
Ectodermal dysplasia	*TP73L*	*hth*§ ($e<10^{-7}$)	Cell cycle	

*An extended version of this table with additional disease categories can be found online. All e-values $<10^{-20}$ unless otherwise indicated. ‡Mild heterozygotes and strong null phenotypes. GAP, GTPase-activating protein; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PTEN, phosphatase and tensin homologue; RAS-V12, a constitutively active form of RAS; RHEB, RAS homologue enriched in brain; RTK, receptor tyrosine kinase; TOR, target of rapamycin. §*D. melanogaster* genes for which mutant as well as wild-type alleles have been isolated.

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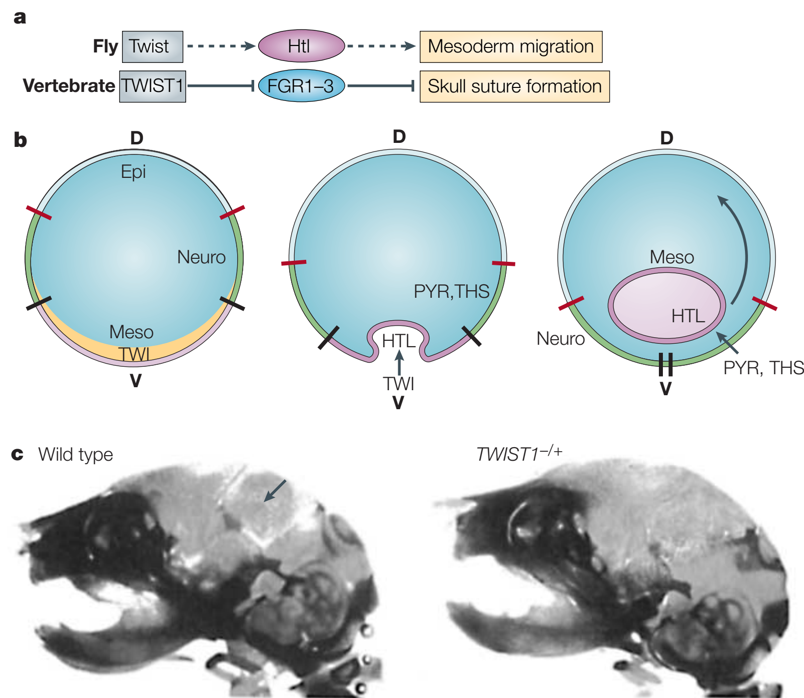

Figure 1 | **Comparison of Twist and FGFR signalling in flies and vertebrates. a** | In flies, Twist activates mesoderm-determining genes such as *heartless* (*htl*), which encodes the fibroblast growth factor receptor (FGFR); by contrast, in vertebrates, TWIST1 signalling represses the activation of FGFR1–3 in key locations such as in the future sutures of the skull. **b** | In the early *D. melanogaster* blastoderm-stage embryo, the nuclear factor κB (NF-κB)-related transcription factor Dorsal (not shown) activates expression of *twist* (*twi*) in the ventral cells (yellow) that give rise to mesoderm (Meso, purple domain). TWI functions as a general activator of mesodermal genes, including *htl*. During gastrulation, the mesoderm invaginates to form a mass of cells under the neural ectoderm (Neuro, green domain). Neuroectodermal cells express two related FGF ligands, Pyramus (PYR) and Thisbe (THS), which activate HTL signalling in the underlying mesoderm (straight arrow) to induce the dorsal migration of mesodermal cells (upwards arrow). Epi, epidermis; D, dorsal side of embryo; V, ventral side of embryo. **c** | In mice, the NF-κB related transcription factor RELA activates expression of *TWIST1*. TWIST1 negatively feeds back to repress activation of RELA target genes, and during formation of sutures in the skull, TWIST1 similarly represses expression of *FGFR2*. In *TWIST1*$^{+/-}$ heterozygous mutants, *FGFR2* misexpression suppresses the formation of coronal sutures, leading to CRANIOSYNOSTOSIS. In humans, similar phenotypes associated with Saethre–Chotzen syndrome result from a reduction in TWIST1 function or from ectopic activation of FGFR signalling. Skulls in **c** reproduced, with permission, from *Nature Genetics* REF. 186 © (1997) Macmillan Magazines Ltd.

COMPLEX GENETIC TRAIT
A measurable phenotype, such as disease status or a quantitative character, that is influenced by many environmental and genetic factors, and potentially by interactions in and between the factors.

DYSMORPHOLOGIES
Diseases resulting in morphological defects.

CRANIOSYNOSTOSIS
Premature fusion of one or more cranial sutures, often resulting in an abnormal head shape.

SYNDACTYLY
Fused digits.

Developmental disorders

DYSMORPHOLOGIES comprise one of the largest and most prevalent groups of human genetic disorders, and have been found, in many cases, to be caused by mutations in genes that control pivotal steps in development. Some of these genes encode transcription factors, which directly control the expression of an array of downstream target genes. In other instances, they encode proteins that function in signal transduction cascades to alter gene expression indirectly or influence post-transcriptional processes such as regulating cytoskeletal structure. Consistent with many of these genes having essential functions in early development, disease phenotypes, which by definition manifest only after live birth, are often caused by only partial loss-of-function alleles. For example, disease can manifest in individuals that are heterozygous for strong or null alleles of the gene responsible or that are homozygous for weak hypomorphic alleles.

In this section, I consider two broad categories of genes causing developmental disorders that can be studied effectively in *D. melanogaster*: genes that have homologous functions in the development of conserved structures present in both humans and flies, and genes that function as part of a conserved genetic pathway that is used for different developmental purposes in humans and flies.

Conserved genes functioning in orthologous capacities. Consistent with there having been a high degree of evolutionary conservation in genetic pathways underlying similar developmental programs in vertebrates and invertebrates, mutations in human homologues of such developmental genes often affect the same tissue or cell type as that affected during *D. melanogaster* development. For example, in line with their developmental roles in *D. melanogaster*, mutations in human Hox genes cause SYNDACTYLY or spinal defects by altering anterior–posterior positional identities; mutations in *PAX6* (*eyeless* in *D. melanogaster*) and *SALL1* (homologous to *salm* and *salr* in *D. melanogaster*) cause defects in the eye and auditory system respectively; mutations in *TWIST1* (*twist* (*twi*) in *D. melanogaster*) lead to malformations of mesodermal derivatives; and *NKX2-5* (*tinman* in *D. melanogaster*) mutations cause defects in heart specification and function (TABLE 1 and see online supplementary information S1 (table). As transcription factors function by regulating the transcription of target genes, these genes probably control the expression of similar sets of effector genes. It should be noted, however, that the effects on the transcription of target genes are not always the same in flies and vertebrates. For example, the *D. melanogaster* Dorsal protein, a nuclear factor κB (NF-κB)-related transcription factor, activates expression of *twi*[7]. In *D. melanogaster*, TWI functions predominately as an activator of mesoderm genes[7–11] such as the fibroblast growth factor receptor (FGFR) gene *heartless*[12,13] (FIG. 1a), which is required for the migration and ultimate specification of heart progenitors (FIG. 1b). In mice, however, TWIST1 seems to function as a negative regulator of the *Fgfr2* gene[14] (FIG. 1a), which is required for the formation of cranial sutures (FIG. 1c). Similarly, vertebrate TWIST1 represses the cytokine gene expression that is induced by the NF-κB-related transcription factor RELA[15], whereas in *D. melanogaster*, TWI and Dorsal synergize to induce gene expression[16]. Also, in humans, both a reduction in TWIST1 function and gain-of-function fibroblast growth factor receptor (*FGFR1–3*) mutations lead to Saethre-Chotzen-like phenotypes (TABLE 1 and see online supplementary information S1 (table). Therefore, in flies, TWI activates the important mediator target FGFR , whereas it apparently negatively regulates the comparable relevant targets in vertebrates. The detailed nature of target regulation by Hox genes — *PAX6*/*eyeless* and *NKX2-5*/*tinman* — also differ between flies and vertebrates, although in general terms their protein products function by homologous mechanisms to define cell fates and/or to control localized cell proliferation (reviewed in REF. 6). In such cases, it could be that recognition of specific DNA binding sites in

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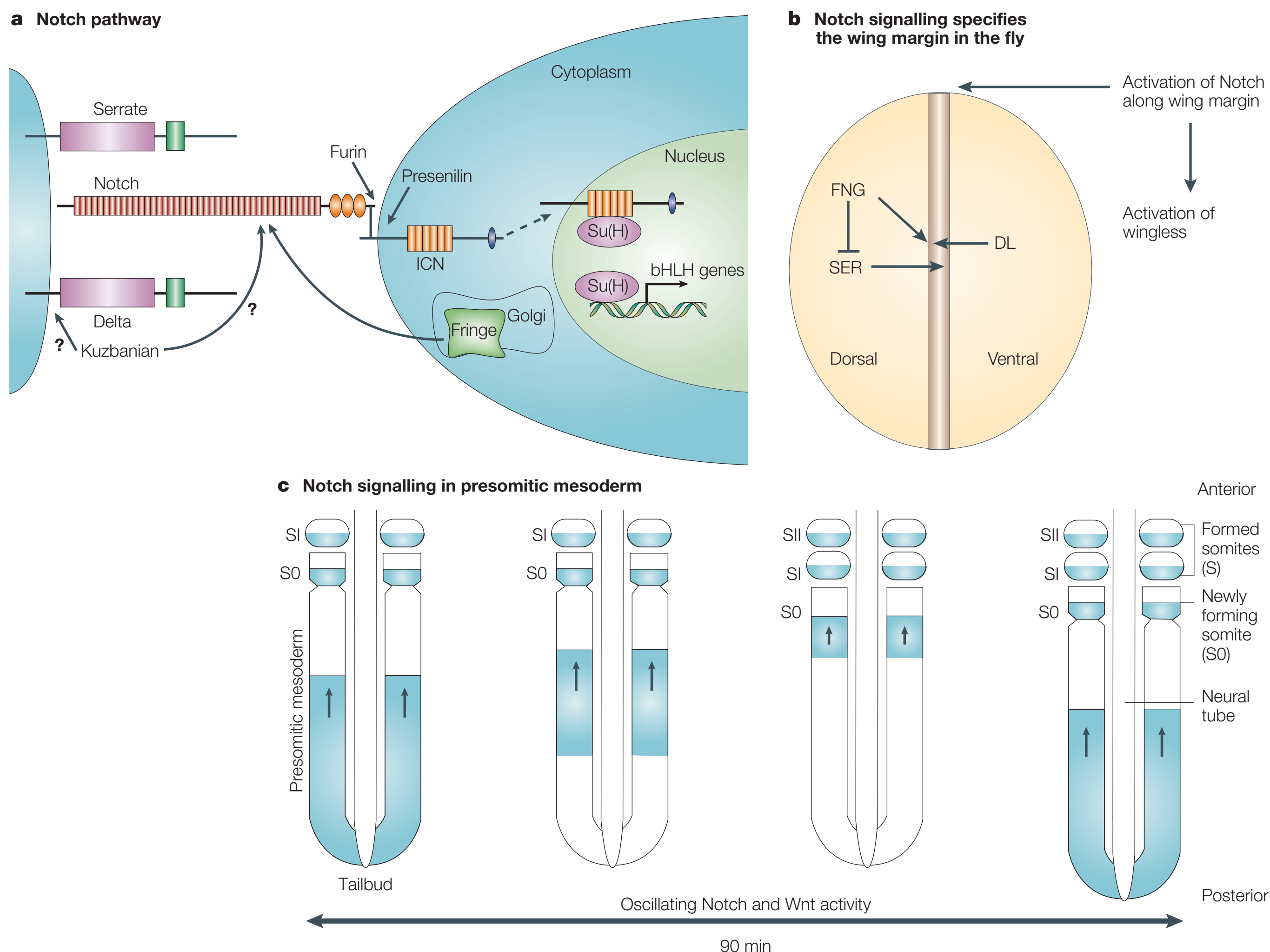

Figure 2 | **The Notch signalling pathway. a** | Signalling by the Notch receptor (shown here in *Drosophila melanogaster*) is initiated by the binding of the receptor to one of two membrane tethered ligands, Delta or Serrate. This leads to a series of specific cleavages of the Notch protein by proteases such as Kuzbanian, Furin, and Presenilin in the extracellular and transmembrane domains, and subsequently to the liberation of the cytoplasmic domain of Notch (ICN). The Suppressor of Hairless (Su(H)) protein binds to the ICN and, following the ligand-induced cleavage of Notch that releases the ICN from the cell surface, a complex consisting of Su(H)-ICN translocates to the nucleus. Here, it activates the expression of target genes, including basic helix–loop–helix (bHLH) genes such as those of the enhancer of split (E(spl)) complex in *D. melanogaster* or Hairy-related proteins in vertebrates. Fringe (a UDP-glycosyltransferase) glycosylates Notch, making it relatively more sensitive to Delta and less sensitive to Serrate. Additional components of the pathway, which are not shown, include Neuralized, a RING-type E3 ubiquitin ligase that targets Delta for proteosome mediated degradation[134], and Mastermind, which encodes a transcriptional co-activator that functions together with Su(H)-ICN[135]. **b** | In the wing IMAGINAL DISC of the third larval instar, Notch signalling is induced in two rows of cells that flank the presumptive wing margin by reciprocal activation by the Delta (DL) and Serrate (SER) ligands. On the dorsal surface, Fringe (FNG) modifies Notch and makes it more sensitive to DL, which is expressed in cells in the ventral compartment, and less sensitive to SER, which is expressed dorsally. In dorsal cells, this configuration of receptor and ligands creates bi-directional signalling across the margin in which Notch signalling is induced adjacent to the dorsal–ventral boundary by DL, whereas in ventral cells Notch remains unmodified by FNG and is activated by SER. Notch signalling then activates expression of the secreted WNT-related *wingless* gene, which organizes gene expression in the vicinity of the wing margin. **c** | Segmentation of the vertebrate somitic mesoderm depends on an oscillating pattern of Notch and wingless related (Wnt)/Fibroblast growth factor (FGF) signalling that spreads along the anterior–posterior axis (blue shading) after being initiated in posterior-most cells. Notch signalling results in the expression of the Hes1 and Hes7 bHLH proteins, which then feedback negatively to inhibit Notch activation of Hes1 and Hes7 and Lunatic Fringe, allowing for FGF stimulated Wnt signaling to initiate another round of the cycle[136–138]. PSM, presomitic mesoderm. Parts **a** and **c** modified, with permission from *Nature Reviews Genetics* REF. 136 © (2001) Macmillan Magazines Ltd.

IMAGINAL DISC
An epithelial sheet of cells that forms as a sac-like infolding of the epithelium in the larva. Small groups of imaginal disc founder cells arise in the embryo. They continue to divide until pupation, when they differentiate into many adult structures (wings, legs, eyes, antennae, genitalia) and then fuse in a quilt-like pattern to construct the adult.

the *cis*-regulatory regions of target genes has been conserved during evolution, but that the final output of the enhancer element containing these sites has changed as a consequence of natural selection.

Conserved genes functioning in different capacities. Some signalling pathways that are common to humans and *D. melanogaster* are used several times during development and might also control species-specific

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Box 2 | **Why do triplet-repeat diseases result in such different disease phenotypes?**

One important unresolved question regarding triplet-repeat diseases concerns how the mutant proteins cause such diverse phenotypes. Do mutant proteins have specific effects on the brain other than those caused by the general cytotoxicity associated with mis-folded proteins in inclusion bodies? On the one hand, the various triplet-repeat diseases have quite different phenotypes, often affecting different parts of the brain. As these proteins are widely expressed in the brain, it is unlikely that the specific defects simply reflect qualitatively different regions of gene expression. Consistent with the view that triplet-repeat diseases cause different defects, distinct subsets of second-site modifier loci have been identified in screens for fly mutants that alter the retinal degeneration phenotypes caused by over-expression of portions of the ataxin 1 (ATXN1), ATXN3, or huntingtin proteins. On the other hand, the toxic effects of these proteins in *Drosophila melanogaster* and in mice can be reproduced with highly truncated proteins or by expressing polyglutamine domains alone. It is possible that the generalized toxicity of polyglutamine proteins involves the depletion of endogenous levels of CHAPERONINS, as reduction in the heat-induction response alone can lead to neural degeneration[120]. It is also unclear whether RNA-based mechanisms, such as that mediated by infantile onset spinocerebellar ataxia (IOSCA), are also involved in the aetiology of other triplet-repeat disorders.

One way to reconcile the general and specific effects of expanded triplet repeats is to assume that the phenotypes of different diseases are a composite of general defects; this would result from cytotoxicity and from specific defects associated with the creation of non-functional aggregates of normal and mutant versions of a particular polyglutamine protein. This latter, more specific, phenotype would be equivalent to expressing a DOMINANT-NEGATIVE ALLELE of the gene in question. Indeed, there is evidence in the case of spinobulbar muscular atrophy (SBMA) that the human disease phenotype includes a component that has a similar effect as loss of function for the *SBMA*-gene product (an androgen receptor)[121]. Alternatively, the specific effects observed in the different diseases could reflect subtle variations in the level of gene expression in different regions of the brain, or varying degrees of functional redundancy between these and related genes in different regions of the brain. This will be an important point to resolve in future studies.

processes. For example, the Notch pathway is involved in defining the dorsal–ventral boundary of appendages in *D. melanogaster* and in establishing the comparable APICAL ECTODERMAL RIDGE in vertebrate limbs. In both cases, asymmetric signalling is regulated by glycosyl transferases of the Fringe family (reviewed in REFS 17,18)(FIG. 2a,b). The Notch pathway is also used to make other cell-fate decisions in flies and vertebrates, some of which are clearly species-specific. For example, in vertebrates, Notch signalling is essential for the proper segmentation of the somitic mesoderm that gives rise to skeletal elements (FIG. 2c), whereas in flies, Notch signalling has a prominent function in limiting the width of wing veins, discussed below. As these are vertebrate- and dipteran-specific structures, respectively, no similarities based on homology can pertain to the development of these particular morphological elements. Nonetheless, relevant inferences can be drawn from one system and applied to the other. For example, mutations in the *Delta* gene (which encodes a cell-surface ligand for the Notch receptor) were first identified in *D. melanogaster*, based on a thickened wing-vein phenotype[19]. Subsequent studies in mice showed that loss of function of the Delta-like 3 (REF. 20), or the lunatic fringe[21,22] genes result in related spinal malformations. In turn, these mouse results have served as a guide for human genetic studies, revealing that similar spinal abnormalities associated with the human diseases Alagille syndrome and spondylocostal dysostosis result from mutations in the human *Delta* homologues jagged 1 (*JAG1*)[23,24] and delta-like 3 (*DLL3*)[25], respectively. Other components of the Notch pathway that have been identified in *D. melanogaster* (FIG. 2a) probably also function during mesoderm formation in vertebrates; these are therefore good candidates for genes that cause phenotypes similar to those that arise as a result of mutations in *JAG1* and *DLL3*.

The ability to identify and place genes in a hierarchical sequence on the basis of EPISTASIS experiments is a clear advantage of fly models. This can then motivate the search for mutations in related genes located in human chromosomal intervals that are associated with similar disease phenotypes.

Neurological disorders

Triplet-repeat diseases. Neurological disorders have been particularly amenable to analysis in *D. melanogaster* (reviewed in REFS 26–30). Perhaps the best studied example is that of triplet-repeat diseases, in which the number of consecutive copies of the glutamine encoding triplet CAG is increased[27,28,31]. This class of expanded triplet-repeat diseases includes the spinal cerebellar ataxias (SCA1, SCA3 and SCA8), Huntington disease (HD) and spinobulbar muscular atrophy (SBMA); in all of these disorders, expansion of triplet repeats leads to neuronal degeneration, but in distinct areas of the brain (BOX 2). As mentioned above, the onset of neuronal degeneration induced by expression of mutant forms of these proteins in the fly retina mimics the retinal degeneration of the disease in humans, with longer repeats resulting in progressively earlier onset times. In addition, inclusion bodies are observed in *D. melanogaster* retinal neurons that express proteins with expanded polyglutamine tracts. Several second-site modifier screens carried out in *D. melanogaster* have identified genes that operate in retinal degeneration; it is hoped that that these genes regulate the formation or clearance of inclusion bodies[32–37]. One class of proteins that has been identified in such screens are heat shock proteins, such as HSP70 and HSP40 , which act as chaperonins that refold mis-folded proteins (FIG. 3a–c). Proteins involved in protein degradation, histone deacetylation and apoptosis have also been identified in several

CHAPERONINS
A class of ring-shaped, heat-shock proteins that have a key role in protein folding and protection from stress.

DOMINANT-NEGATIVE ALLELE
A form of mutation that interferes with the function of its wild-type gene product.

APICAL ECTODERMAL RIDGE
The thickening of the ectoderm at the tip of a developing chick limb bud, which is required for bud outgrowth.

EPISTASIS
The situation in which the phenotype caused by a mutation in one gene is masked by a mutation in another gene. Epistatic analysis requires that two mutants have distinguishable phenotypes. It can be used to determine the order of gene function by testing whether the phenotype of the double mutant *ab* is similar to that of mutant *a*, or mutant *b*.

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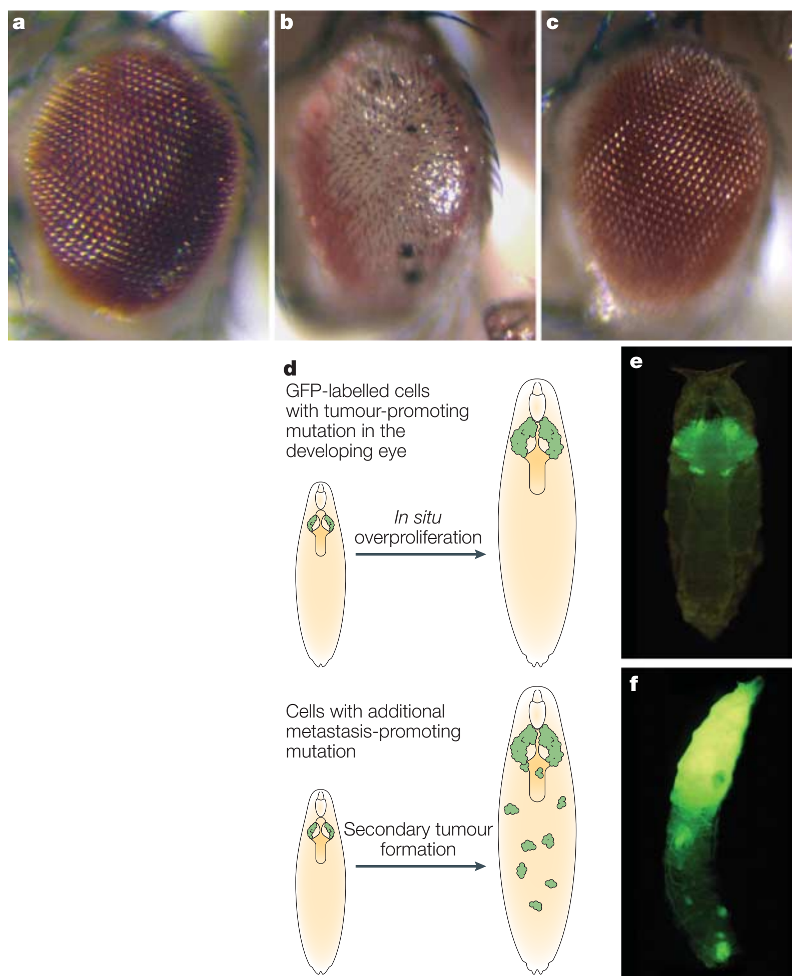

Figure 3 | **Examples of second-site modifier screens in *Drosophila melanogaster*.** Suppression of polyglutamine-induced retinal degeneration. **a** | A control eye expressing the human HSP70 protein (HSPA1L) under the control of the GMR driver (an enhancer that drives expression specifically in the eye). **b** | A degenerating eye expressing a protein with an expanded polyglutamine domain, MJDtr-Q78, under the control of GMR. This mutant protein contains a domain of 78 glutamines in place of the normal run of 27 residues. **c** | Co-expression of the human chaperonin HSPA1L with MJDtr-Q78 results in suppression of the retinal degeneration phenotype caused by MJDtr-Q78 alone (see **b**). **d–f** | Screening for mutations that cause metastasis of RAS-transformed cells. Genetic scheme (**d**) in which flies expressing activated RAS-V12 and green fluorescent protein (GFP, shown in green) in the eye (top scheme in **d** and part **e**) are screened for second-site mutations that allow cells to spread from the head to other regions of the body (bottom scheme in **d**, and part **f**), including the ventral nerve chord and other sites. Parts **a–c** reproduced with permission from *Nature Genetics* REF. 33. © (1999) Macmillan Magazines Ltd. Parts **d–f** reproduced with permission from REF. 99 © (2003) American Association for the Advancement of Science.

different modifier screens. Some of these interacting pathways are also relevant in vertebrates, as expression of *HSP70*[38–40] or inhibitors of histone deacetylases[41] in mice can reduce the effects of expressing expanded polyglutamine domain proteins. In addition, genes encoding RNA-binding proteins have been recovered in screens for modifiers of the degeneration caused by expression of the human *SCA8* (also known as *IOSCA*) non-coding RNA[42]; this indicates that expanded triplet repeats are likely to cause toxicity at both the RNA and protein levels. The fly retinal degeneration models can also be used to validate the activity of small molecule candidates that might be used as therapeutic agents. For example, histone deacetylase inhibitors[32,36,41] as well as a compound that enhances the heat shock response[43] suppress phenotypes caused by overexpressing mutant polyglutamine proteins.

Parkinson disease. The function of genes involved in Parkinson disease (PD), which causes progressive loss of dopaminergic neurons in the brain stem, has been analysed in *D. melanogaster*. In humans, the best studied gene, *SNCA*, encodes the neuronal protein α-synuclein, which is present in presynaptic terminals[44]. The mutations in *SNCA* that cause PD lead to the formation of cytoplasmic aggregates known as Lewy bodies[45], which differ in location and quality from the predominantly nuclear inclusion bodies found in neurons that express expanded polyglutamine domain proteins. Although flies do not have an obvious homologue of *SNCA*, misexpression of the mutant but not normal forms of the human protein results in late-onset neurodegeneration in the fly eye[46]. Modifier screens of this neural degeneration phenotype have identified a set of genes that interact with α-synuclein; this set overlaps with genes identified as interactors with polyglutamine disorders such as *HSP70*, but also includes a distinct subset of genes. It is possible that the interaction of the identified genes with HSP70 results from a general depletion of the endogenous chaperonin pool (BOX 2). Alternatively, the specific set of interacting genes might implicate pathways that are more directly involved with *SNCA* (although it is of some concern that *D. melanogaster* does not contain an obvious α-synuclein-related protein).

The ubiquitin pathway has also been implicated in regulating the accumulation of α-synuclein, because mutations in the human *PARK2* gene, which encodes the ubiquitin E3-ligase parkin[47,48] and causes PD when mutated, is normally found in a complex with a form of α-synuclein, and both of these proteins have been found in Lewy bodies. However, mutant disease forms of parkin do not associate with α-synuclein, indicating that loss of *PARK2* function leads to α-synuclein accumulation. Mutations in the conserved fly homologue of *PARK2* – *park* – cause degeneration of certain flight muscles and hypersensitivity to free radicals[49], phenotypes that are reminiscent of the known sensitivity of dopaminergic neurons to toxin induced degeneration. Overexpression of *park* can reduce the effect of α-synuclein in the *D. melanogaster* eye[50,51] and suppress the neuronal degeneration caused by production of another substrate for parkin, PAELR[51]. Further analysis should shed light on the relationships between these various proteins and other potential proteins targeted for degradation by parkin.

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Familial Alzheimer disease. Genes mutated in familial Alzheimer disease (FAD) have been well-studied in flies. The unique *D. melanogaster* gene that is homologous to the two human Presenilin (PSN) genes (*PSEN1* and *PSEN2*) can be mutated to cause early onset FAD[52,53]. Presenilins are transmembrane proteases that form the catalytic core of γ-secretases; this core cleaves various substrates, which include β-amyloid (APP)[54], a transmembrane protein that is a principal component of the extracellular AMYLOID PLAQUES that accumulate in the brains of FAD patients. Mutations in the human *APP* gene also cause FAD[55–57], and mutant forms of PSN lead to the accumulation of the aberrant secreted APP peptides that are found in plaques. *Drosophila melanogaster* also has a homologue of the *APP* gene (*Appl*), which when mutated leads to premature death. Several potential normal functions for APP have been suggested, including: mediating cell-surface signalling[58–62], functioning as a receptor for the kinesin-dependent transport of specific cargo molecules along axons[63,64] and binding Cu^{2+} and reducing its neurotoxicity[65], although it is unclear whether disruption of any of these functions contributes to FAD. Another substrate of PSN, which has been well-studied in *D. melanogaster*, is the Notch receptor (reviewed in REF. 66); however, it remains to be determined whether Notch is an important target of Presenilins in the aetiology of FAD.

Drosophila melanogaster and *Caenorhabditis elegans* have also been used effectively to identify other proteins involved in PSN activity. One such protein is nicastrin[67–71], which forms part of the γ-secretase complex in both organisms. Therefore, further analysis of this elusive pathway in *D. melanogaster* will probably provide more insights in this developing field.

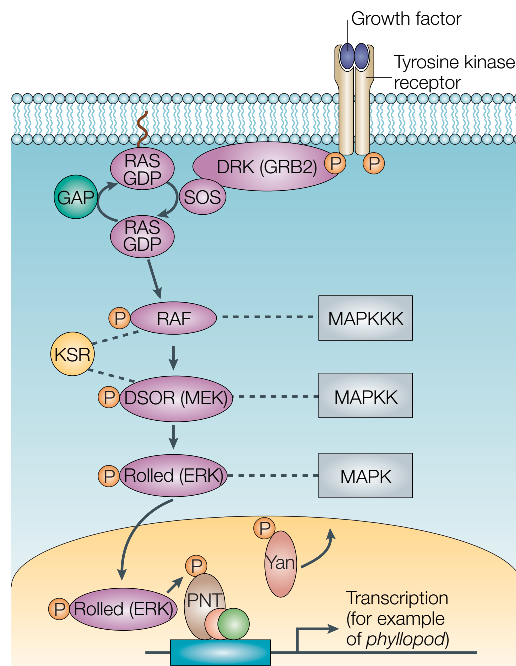

Figure 4 | **The canonical receptor tyrosine kinase (RTK) signalling pathway.** RTK signalling is initiated by the binding of a ligand to monomeric forms of the receptor, leading to receptor dimerization. Dimerization of receptors typically leads to cross-phosphorylation (P) of the two chains, thereby creating a docking site for the SH2 domain of the adapter protein downstream-of-receptor-kinase (DRK; also called GRB2). Through an interaction with its SH3 domain, DRK recruits the guanine nucleotide exchange factor Son-of-Sevenless (SOS) to the cell surface, which then catalyses the exchange of GDP for GTP for RAS, increasing the level of active RAS-bound GTP. Activated RAS leads to a chain of phosphorylation of the cytoplasmic RAF, DSOR and then Rolled. When Rolled/MAPK is doubly phosphorylated by DSOR/MAPKK, it becomes activated (MAPK*) and translocates from the cytoplasm to the nucleus; here, it phosphorylates transcription factor targets such as the Ets-domain proteins Pointed (PNT) and Yan. MAPK*-dependent phosphorylation of PNT converts it from an inactive form to a transcriptional activator, while phosphorylation of Yan inactivates it as a repressor. These concerted actions of MAPK* lead to activation of transcriptional targets such as Phyllopod in the R7 photoreceptor cell. The scaffolding protein KSR interacts with RAF and DSOR to promote signalling in this pathway. GAP, GTPase-activating protein. Diagram modified with permission from *Nature Reviews Molecular Cell Biology* REF. 139 © (2004) Macmillan Magazines Ltd.

Fragile X syndrome. Fragile X syndrome results from the expansion of the non-coding triplet CGG repeat and loss of function of the *FMR1* gene (reviewed in REF. 72). *FMR1* encodes an RNA-binding protein that negatively regulates the translation of several target genes such as *MAP1B* (*futsch* in *D. melanogaster*)[73] and genes encoding other proteins that function at the synapse required for normal dendritic morphology[74]. Studies on flies have yielded two important contributions to the understanding of fragile X syndrome. First, biochemical analysis of proteins associated with the *D. melanogaster* homologue of *FMR1* (*Fmr1*)[75], showed that components of the RNA INTERFERENCE (RNAi) pathway form a complex with FMR1. This led to the demonstration that a reduction in these components, such as Argonaute (AGO1), is essential for the function of FMR1: reduction in AGO1 levels could suppress the apoptosis phenotype caused by *Fmr1* overexpression and could enhance in a dominant manner the phenotype of *Fmr1* loss-of-function mutations[76]. Another interesting question regarding fragile X syndrome is why heterozygous carriers for the mutant triplet expanded gene suffer from neuronal degeneration whereas homozygous individuals who do not express *FMR1* have mental retardation but no neurodegeneration. Using the fly eye as an assay system, it was observed that expanded, non-coding G triplets, but not wild-type numbers of these triplets, could cause neuronal degeneration in the eye, thereby mimicking the situation in humans[77]. This effect could be produced by purely non-coding sequences, providing the first clear evidence that the neural degeneration phenotype could be mediated exclusively at the RNA level. This result is consistent with the more recent finding that neuronal degeneration can be caused by expansion of the non-coding CAG triplet in the *SCA8* transcript (described above). In addition, expression of *HSP70* ameliorated the phenotype induced by the non-coding

AMYLOID PLAQUES
Extracellular, insoluble aggregations of amyloid β-peptide$_{42}$ fragment, cleaved from the amyloid precursor protein, that accumulate in the brains of Alzheimer disease patients.

RNA INTERFERENCE
A process by which double-stranded RNA specifically silences the expression of homologous genes through degradation of their cognate messenger RNA.

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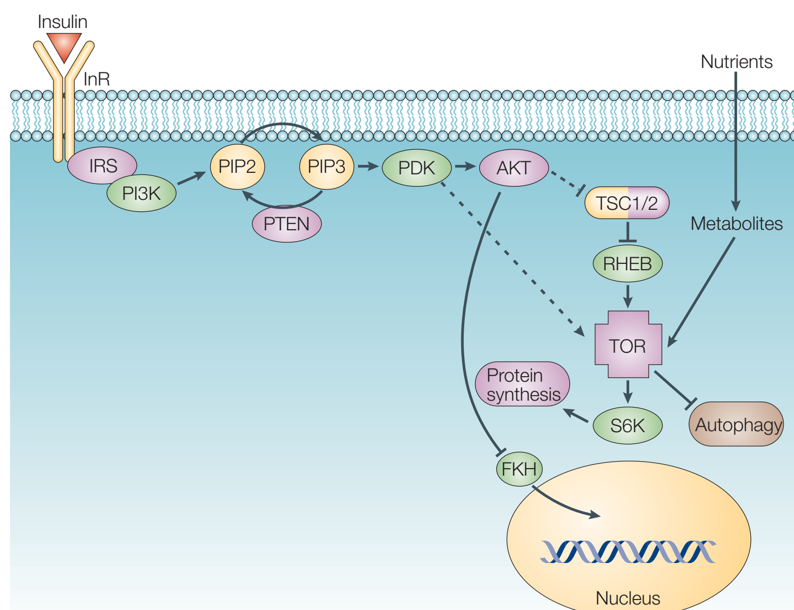

Figure 5 | **The target of rapamycin (TOR) pathway.** The TOR pathway has a central role in organizing cell growth. The TOR kinase is activated by two inputs: the Insulin pathway and by extracellular nutrients. Insulin signalling through the insulin receptor (InR) is mediated by the cytoplasmic insulin receptor substrate (IRS), which leads to activation of phosphoinositide-3-kinase (PI3K) and conversion of phosphatidylinositol 3,4-biphosphate 2 (PIP2) to PIP3. PIP3 functions as a co-factor to stimulate PDK (pyruvate dehydrogenase kinase) and activation of the AKT1 (v-akt murine thymoma viral oncogene homologue 1) kinase. The phosphatase and tensin homologue (PTEN) phosphatase opposes the activity of PI3K by converting PIP3 back to PIP2. AKT suppresses the activity of the tuberous sclerosis 1 (TSC1)/TSC2 complex, which inactivates the RAS-related TOR inhibitor, RAS homologue enriched in brain (RHEB). AKT also phosphorylates Forkhead/Foxo (FKH) transcription factors, preventing them from gaining entry to the nucleus and activating expression of various target genes including those stimulating apoptosis. TOR is activated by external nutrients by sensing levels of various metabolites such as amino acids, which might involve the regulatory associated protein of TOR (Raptor, not shown). Once activated by Insulin-dependent signalling or nutrient-sensing, TOR phosphorylates effector targets such as S6 kinase and initiation factor 4E-binding protein (4e-BP) to stimulate translation (that is, by activating S6K and inhibiting the negative regulator 4E-BP). TOR also negatively regulates cell autonomous catabolic mechanisms such as autophagy, which can provide amino acids under conditions where external nutrients are limiting.

portion of *Fmr1*, indicating that the triplet RNAs are associated directly or indirectly with the formation of protein aggregates that can be acted on by HSP70.

Cancer

The RTK–RAS–MAPK signalling pathway. Although the short-lived fly does not naturally develop cancer manifested by lethal tumour overgrowth and metastasis, as observed in vertebrates, mutations in *D. melanogaster* genes that affect cell-cycle control and epithelial integrity have been recovered. These genes have roles that are germane to steps in tumour formation and dispersion in humans. One of the first uses of *D. melanogaster* to address issues in human cancer was the paradigm-setting genetic reconstruction of the oncogenic receptor tyrosine kinase (RTK)–RAS–MAPK pathway. This feat was accomplished by a series of second-site modifier screens, originating with the pioneering modifier screen of a weak *sevenless* RTK allele by Simon and colleagues[78]. This and subsequent genetic screens in *D. melanogaster*[79,80], together with similar screens performed in *C. elegans* by Sternberg and colleagues to identify components of the EGF-receptor signalling pathway[81-85], created the first clear link between biochemically defined components and a genetically defined hierarchy. One of the most important insights derived from this analysis was that, to a first approximation, the RTK–RAS–MAPK pathway could be modelled as a linear pathway, in which sequential gene action connected cell-surface RTK receptors to the activation or repression of specific transcription factors in the nucleus (FIG. 4). Before the genetic analysis in *D. melanogaster* and *C. elegans* was carried out, it was not obvious that the observed biochemical interactions defined a single coherent pathway. It is difficult to overestimate the importance of these seminal studies, as they have provided the solid foundation for a flurry of subsequent second-site modifier screens that are now characteristic of model genetic systems. Such screens have identified many of the components of the now well-characterized Wingless, Hedgehog, transforming growth factor-β and Notch pathways, and several of these genes have subsequently been found to be mutated in various human cancers (TABLE 1 and online supplementary information S1 (table).

The target of rapamycin (TOR) pathway. Tuberous sclerosis is a dominantly inherited disorder that is characterized by the formation of benign tumours. It can be caused by mutations in two genes, *TSC1* or *TSC2*, the products of which form a complex that functions as a GTPase-activating protein (GAP) to inactivate the RAS-related protein RAS homologue enriched in brain (RHEB) (reviewed in REF. 86) (FIG. 5). Mutations in the homologous fly genes *Tsc1* and *Tsc2* lead to excessive cell growth (identified as cells that are larger than normal rather than more cells), a phenotype that is mediated by the target TOR signalling pathway[87–89]. Genetic epistasis studies in *D. melanogaster*, in combination with biochemical experiments, support a model in which TSC1, TSC2 and RHEB function with the well-studied insulin pathway to induce TOR signalling, which can also be activated by nutrients[86]. In turn, TOR signalling activates protein synthesis and cell growth while inhibiting catabolic processes such as autophagy[90,91]. Over-activation of the insulin branch of the TOR pathway (reviewed in REF. 92) also causes cancer in humans; this is manifested by mutations in the tumour suppressor gene *PTEN*, which negatively regulates the activity of the insulin pathway mediator phosphatidylinositol 3-kinase (PI3K). As with *Tsc1* and *Tsc2*, mutations in the fly *PTEN* homologue result in the overgrowth of cells. In this complex and fast moving field, *D. melanogaster* has had an integral role in establishing and testing models for the control of cell growth by insulin and nutrients.

Cell-cycle control. Control of the cell cycle has also been well studied in flies. Forms of cancer caused by the disruption of components acting at check points that negatively regulate the cell cycle under normal conditions, can be modelled and analysed in flies. *Drosophila melanogaster* has homologues of genes encoding

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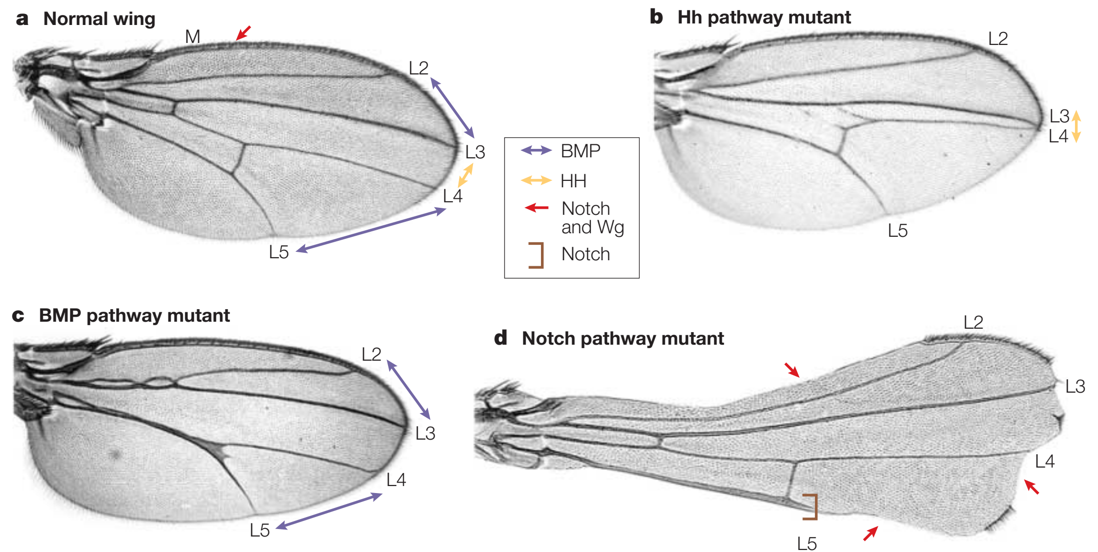

Figure 6 | **The *Drosophila melanogaster* wing provides an assay system for several signalling pathways. a** | A wild-type wing with the wing margin (M) and the longitudinal veins L2–L5 indicated. The spacing between the L3 and L4 veins is determined during the second and third larval instars by hedgehog (HH) signalling (yellow double arrow), whereas the spacing of the L2–L3 and L4–L5 veins is determined by bone morphogenetic protein (BMP) signalling (blue double arrows). The margin, which forms at the interface between the dorsal and ventral compartments of the wing (FIG. 2b), forms in response to a reciprocal form of Notch induction that leads to production of the wingless (WG) morphogen along the margin (Notch and WG signalling indicated by red arrow). **b** | A wing in which reduced HH signalling has selectively narrowed the spacing between the L3 and L4 veins (yellow double arrows). **c** | A wing in which reduction of BMP signalling has selectively reduced the distances between the L2–L3 and L4–L5 veins leading to partial fusion of these vein pairs (blue double arrows). **d** | A wing with reduced Notch activity exhibiting both notches in the wing margin (red arrows) and thickened veins (bracket on L5 vein; L3 is also broader than normal). This combination of wing margin nicks and thickened veins is diagnostic for a defect in Notch signalling, whereas defects in the wing margin alone might indicate reduced WG signalling. Part **d** reproduced, with permission, from REF. 187 © 1995 Company of Biologists.

components that promote the cell cycle; these include cyclins, cyclin dependent kinases (CDKs) and E2F genes, as well as inhibitors such as CDKN2B (also called P15 and Decapo), CIB1 (also called KIP), and the retinoblastoma protein RB1 (reviewed in REF. 93). *D. melanogaster* also has a homologue of p53, a downstream pro-apoptotic effector of E2F genes. One important advantage of *D. melanogaster* for analysing the intricate interactions between these various cell-cycle components is that flies typically have only one copy of these genes. By contrast, vertebrate cells often express several related proteins of each component. Genetic analyses of these genes in flies have been largely consistent with those in vertebrates (although with some notable exceptions). In addition to *D. melanogaster* being an excellent system for dissecting the control of the cell cycle, genetic screens for so-called 'tumour-suppressor' mutants that lead to cellular overgrowth, such as those that identified mutations in *TSC1*, *TSC2* and *PTEN* mentioned above, have been carried out in *D. melanogaster* and have identified mutations affecting previously unknown negative regulators of the cell cycle such as Warts (WTS, also known as LATS)[94,95], Salvadore (SAV)[96] and Hippo[97]. Identification of the *wts* and *sav* genes in *D. melanogaster* has motivated studies in mice or humans that confirm the importance of these genes in mammalian tumorigenesis. *Lats1* mice develop tumorous overgrowths similar to those identified in the fly and to human renal and colon cancer cell lines that carry mutations in the *sav* homologue. Analysis of these genes in *D. melanogaster* has indicated the mechanisms by which they act, as the *wts*, *sav*, and *hippo* products physically interact[97] and mutants in each of these genes lead to elevated levels of cyclin E as well as the apoptosis inhibitor DIAP1. Therefore, studies in flies have not only helped to clarify the mechanisms by which the cell cycle is regulated, but have also lead to the identification and characterization of new genes involved in preventing excessive cell proliferation and cancer formation in mammals.

Tumour metastasis. Another area of human disease on which fly genetics might shed some light is tumour metastasis. Although tumour metastasis has not been observed in wild-type flies, the regulation of cell behaviours such as the migration and invasion of epithelial sheets will probably show mechanistic similarities to those processes involved in the multi-step spread of cancer cells. For example, some normal cells, such as embryonic blood cells, ovarian border cells and cells comprising both somatic and germline components of the gonad, undergo programmed migrations followed by the invasion of an epithelial sheet (reviewed in REF. 98). These two distinct developmental steps have been studied by various means, and genes required for each process have been identified. In addition, a screen to identify mutants that result in the metastatic spread of RAS-transformed cells identified mutations in the *scribbled* (*scrib*) gene, which is required to maintain normal apical-basal

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Box 3 | Limitations of flies in analysing human disease

Although one of the main objectives of this review is to illustrate the range of uses of *Drosophila melanogaster* as a tool for human genetics, it should be acknowledged that there are limitations in any invertebrate system, particularly with regard to biological processes that have evolved only within the vertebrate lineage. For example, genes involved in creating the four chamber heart, in elaborating the coordinated system of ducts in mammary glands, or in the condensation of chondrocytes to synthesize calcified bone, would not be ideal targets for study in *D. melanogaster*. However, as mentioned previously, genes involved in specific steps in these processes might have conserved functions within ancestral genetic pathways, and their function within those pathways could be studied productively in *D. melanogaster*. For example, in the case of spinal malformations, flies could not be used to model bone formation *per se*, but as Notch signalling has a pivotal role in regulating this process, any knowledge obtained about interactions between components of this pathway in flies might be relevant to processes that these genes control during spinal formation in humans.

In other cases, simpler model systems such as yeast might offer advantages over *D. melanogaster*; these include shorter generation times, smaller genomes, and larger numbers of individuals that can be produced, scored or selected in genetic screens. Highly conserved genes that cause the many known metabolic disorders or genes involved in regulating cell autonomous functions, such as DNA repair, represent examples of this. Nevertheless, although yeast might be the most powerful genetic organism for addressing questions about the cell autonomous functions of such genes, the fly can often complement these studies and can be used to model aspects of the disease that are manifest at the level of a tissue or that involve communication between cells. For example, many metabolic disorders cause neurological defects, presumably because neurons are most sensitive to reductions in the activity of these general processes, such as energy metabolism. Similarly, defects in mismatch repair cause cancer in humans and can also be modelled at the whole-organism level in flies. Indeed, it could be argued that the ideal approach to studying a human disease would be to pursue parallel analysis of the gene using all relevant tiers of model organisms; for example, cell-autonomous effects of the gene could be studied in yeast, multicellular or inductive events mediated by that gene in *D. melanogaster* or *Caenorhabditis elegans*, and an accurate disease model for mutations in that gene could be developed using mice.

There are also examples of where a process common to vertebrates and invertebrates has been studied from a genetic point of view in *D. melanogaster*, but the relevance of these studies with regard to human disease remains to be determined. For example, pioneering work by the Benzer group in the field of ageing has identified several genes such as *drop dead*[122,123], *Cysteine string protein*[124], *swiss cheese*[125] and *methusla*[126], but so far there is no evidence that mutations in human homologues of these genes lead to premature ageing. On the other hand, future studies might reveal that the human counterparts of these genes are involved in ageing, as there is good evidence that genes such as those encoding components of the insulin pathway[127–131] or anti-oxidants[132] do seem to influence the occurrence or onset of age-related disorders. Therefore, while it is important to bear in mind the potential caveats and limitations to analysing the function of human disease genes in simpler model systems, it should be emphasized that the fly need not serve as an explicit model for a disease to be of potential value in understanding the mechanistic basis for the disease process.

cell polarity. On their own, *scrib* mutants cause the over-proliferation of cells, as do mutations in the tumour-suppressor loci *lethal(2) giant larvae* (*l(2)gl*) and *discs large* (*dlg*). Production of an oncogenic activated form of *D. melanogaster* RAS (RAS-V12), or loss-of-function mutation of *scrib*, *l(2)gl* or *dlg*, cause the over-proliferation of cells. However, when these conditions are combined in CLONES, cells break free from their site of production (such as the eye) and disperse to other locations such as the nerve cord and trachea[99,100] (FIG. 3d–f). Activating *Notch* mutations can also lead to metastasis when they are combined with *scrib* mutations, although it is unclear how the activation of RAS and Notch provide a similar precondition for metastasis[100]. Metastatic cells are also similar to mammalian tumours in that they downregulate expression of the adhesion molecule E-cadherin, which otherwise prevents this metastasis, and gain an ability to disrupt the extracellular matrix[99]. These observations support the view that invasive cancer results from a series of distinct steps and opens the way to analyse the separate processes of transformation and metastasis in detail.

CLONES
Patches of clonally derived cells in an organism that have been engineered to be genetically distinct from surrounding cells (for example, a homozygous mutant clone in a heterozygous background).

Future perspectives

Closing the loop. On the basis of the successes described above, the future looks very bright for the use of *D. melanogaster* as a tool for identifying and analysing a broad range of human disease genes. Flies may also help to open up several new frontiers. As mentioned in the introduction, one approach is to use *D. melanogaster* in a directed fashion to answer specific questions that are relevant to the human genetics community. For example, in my own group, several such projects are being pursued including: identifying proteins targeted for degradation by the UBE3A ubiquitin E3 ligase, which is mutated in Angelman syndrome[101–103]; showing that two antioxidant proteins, TSA and PAG[104–106] that bind to PSN[107] also interact genetically with *Psn* in *D. melanogaster* and can be considered as candidate genes for causing Alzheimer disease-related diseases; screening for candidate genes corresponding to a known human suppressor locus that can protect individuals in Saudi pedigrees from primary congenital glaucoma caused by mutations in the cytochrome P450 (*CYP1B1*) gene[108,109]; and screening for novel cellular targets of bacterial toxin proteins in *D. melanogaster*. For each of these projects we have collaborators in the field of human genetics who will test candidate genes for specific functions. For example, they can help to determine whether a candidate target of ubiquitin protein ligase E3A is mis-regulated in the brains of mice or humans with Angelman syndrome, whether any of the five *TSA*

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and/or *PAG*-related human genes that map to genomic intervals associated with FAD are mutated in affected individuals, whether human homologues of genes that can suppress mutant phenotypes in the fly homologue of *CYP1B1* are mutated or mis-expressed in unaffected Saudi individuals homozygous for *CYP1B1* mutations, and whether endogenous proteins required for the systemic function of bacterial toxins in *D. melanogaster* interact directly with the toxins or known toxin targets.

Analysis of multigenic disorders. Another crucial area to which flies could contribute is in the analysis of polygenic disorders. The ability to screen large numbers of flies for mutations affecting dispensable structures such as the eye (FIG. 3) or the wing (FIG. 6) allows large numbers of genetic combinations to be analysed. One of the leading strategies to address this important problem is the HapMap initiative (see Online links box)[110], which initially aims to define over 600,000 characteristic human HAPLOTYPES, consisting of tightly linked markers that recombine at very low frequency due to LINKAGE DISEQUILIBRIUM. Completion of the HapMap project should greatly facilitate the identification of new disease genes and define intervals containing genes that function in a combinatorial way to result in healthy or diseased phenotypes. One challenge that will arise from this type of analysis is determining which genes among several plausible candidates at multiple loci contribute most to a phenotype in question. *Drosophila melanogaster* could serve as an ideal experimental tool to test for genetic interactions among many potential loci, as there is already a good precedent for pursuing similar genetic strategies in simpler organisms such as yeast. One such example is a group of congenital disorders of glycosylation (CDG), which affect consecutive steps in the synthesis of carbohydrate chains[111]. In this case, Hennet and colleagues devised a screen that was a phenotypic analysis of a mutant in a yeast CDG homologue[108], and its rescue by the human homologue, which they used to identify unknown genes acting in the same glycosylation pathway in yeast. Subsequently, they found that mutations in the human homologues of these newly identified yeast genes caused CDG[113–115]. Although yeast is a powerful system for scoring genetic interactions between conserved genes acting within single cells, *D. melanogaster* and *C. elegans* are more appropriate genetic models for studying diseases that involve interactions between cells or organ function. Analysis of cardiac disease in flies is particularly attractive in this respect, as *D. melanogaster* is the simplest organism with a pumping heart tube. Furthermore, as mentioned previously, the heart develops by a mechanism that has been highly conserved during evolution[116] and the fly heart is experimentally amenable to physiological testing and manipulation[117,118].

Genomic semantics: translating between different genetic languages. The experimental advantages of *D. melanogaster* could also be exploited in conjunction with bioinformatic approaches. One intriguing possibility is to link genetic processes that are partially defined in both flies and in humans. In *D. melanogaster*, genetic pathways are typically defined by the analysis of loss-of-function mutations that can cause severe phenotypes and lethality (for example, the absence of ventral epidermis in *Notch*$^{-/-}$ mutants). Human diseases, however, are typically defined by much more subtle phenotypes, as they must minimally survive until sometime after birth. Therefore, heterozygous mutations in *Notch* lead to modest spinal malformations. If the phenotypic descriptions of null *D. melanogaster* mutants and the weak, partial loss-of-function human mutations are considered as lexical items in different genetic languages, then it might be possible to devise a translation between these sibling languages, which have diverged over the course of evolution. For example, human diseases could be clustered on the basis of similarities in the controlled vocabulary that is used in the clinical synopses for each disease and ask whether there is any known phenotypic relationship between *D. melanogaster* homologues of these human gene clusters. Similarly, if fly researchers were to create a controlled vocabulary to describe mutant phenotypes, the same type of analysis could be carried out in reverse by asking whether the diseases caused by mutations in the human homologues of *D. melanogaster* genes with related functions shared some previously unappreciated similarities. This genetic semantics approach could, in principle, define many useful leads that could then be tested to identify new functional links between both human and fly gene sets. To make such a potentially powerful analysis possible, an important enabling advance would be the adoption of a controlled vocabulary by the *D. melanogaster* research community.

Genome network modelling and validation. *D. melanogaster* could also be used to sort out potential relationships that are indicated by the analysis of genome-scale datasets, such as those resulting from microarray gene expression analysis or whole-proteome interaction maps. These types of high-throughput methods indicate that there are large numbers of potential interactions, but do so with relatively low predictive confidence. As stock collections that carry mutations in every predicted *D. melanogaster* gene will probably be available soon, comprehensive sets of transheterozygous interaction tests could be designed to validate these predictions. Newly developed multiplex *in situ* hybridization methods[119] (see Online links box) will, in principle, allow one to examine the expression of up to 50 genes at a time in single embryos or tissues. This should help to construct comprehensive gene expression atlases, which, in turn, will aid in decoding gene regulatory networks. These genome-scale relationships can fuel bioinformatic efforts to identify novel genes that contribute to human disease and to link such genes into networks of disease processes.

Summary

Drosophila melanogaster has a broad spectrum of genes that are related to human disease genes and has already proven itself to be a powerful tool for analysing the function of these genes and identifying novel genes that function in disease processes such as developmental disorders, neurological diseases or cancer. Although

HAPLOTYPE
An experimentally determined profile of genetic markers that is present on a single chromosome of any given individual.

LINKAGE DISEQUILIBRIUM
The condition in which the frequency of a particular haplotype for two loci is significantly greater than that expected from the product of the observed allelic frequencies at each locus.

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D. melanogaster will probably not always serve as a perfect model for human disease processes (BOX 3), the fact that shared ancestral molecular interactions and pathways underlie the function of genetic processes in both flies and humans will continue to allow researchers to exploit the fly model to answer existing questions and to pose new hypotheses. In the future, an important focus of human genetics will probably be to determine which genes contribute to complex disorders, and flies will again provide a powerful means to identify such interacting partners and to understand the mechanisms that underlie such interactions. It seems clear that *D. melanogaster* will maintain its status as the golden bug in the foreseeable future.

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Competing interests statement

The authors declare competing financial interests: see Web version for details.

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