Table 1. Numbers and phenotype of lymphoid cells in −/− mice. Thymus and spleen cellularities were determined for 13 −/− mice at ages from 7 to 28 days; representative values are compared with values for control (C) littermates (+/− or +/+). The phenotypes were determined by fluorescence-activated cell sorting; the percentages staining positive are given (–, not determined).

	Cellularity (%) and genotype											
	Total (10^6 cells)		$CD4^+CD8^+$		$B220^+$ (total)		$B220^+sIgM^+$		$CD4^+$		$CD8^+$	
Cells	−/−	C	−/−	C	−/−	C	−/−	C	−/−	C	−/−	C
					Day 7							
Thymus	1.5	46.3	11.6	93.1	–	–	–	–	1.3	0.7	0.1	0.2
Spleen	29.5	35.0	–	–	2.6	22.0	–	–	0.7	2.9	0.1	1.0
					Day 9							
Thymus	0.8	57.0	83.6	93.2	–	–	–	–	9.0	4.7	0.3	0.5
Spleen	21.0	24.0	–	–	2.1	23.2	–	–	0.6	4.9	0.1	1.3
					Day 12							
Thymus	7.6	136.0	86.4	94.8	–	–	–	–	10.5	3.9	0.4	0.6
Spleen	5.8	41.0	–	–	11.6	62.5	9.4	60.2	6.6	9.7	0.4	3.2
					Day 25							
Thymus	12.8	151.0	81.2	88.2	–	–	–	–	11.4	9.3	1.3	1.7
Spleen	22.0	81.0	–	–	12.1	68.7	8.4	63.5	7.0	12.3	0.4	4.8

vating Jak3 (*2*) and inducing the tyrosine phosphorylation and activation of the DNA-binding activity of the signal transducer and activator of transcription 6 (Stat6) (*8*). Gel shift analysis showed that although IL-4–induced Stat6 DNA-binding activity was detectable in splenocytes from the +/+ and +/− mice (Fig. 4B), only a faint activity that was not affected by antisera to Stat6 was induced in splenocytes from the −/− mice. The absence of IL-7 or the IL-7 receptor α chain results in profound effects on lymphoid differentiation (*9*). Because the IL-7 receptor uses the γ_c chain and activates Jak3 as well as Lyn and Fyn (*10*), we examined the response of bone marrow cells to IL-7 (Fig. 4A). No stimulation was observed with bone marrow cells from the −/− mice.

The phenotype of −/− mice is similar to that of mice lacking the γ_c chain (*11*), the IL-7 receptor α chain, or IL-7 (*9*), consistent with the hypothesis that the interaction of IL-7 with its receptor and the activation of Jak3 are critical, nonredundant functions in lymphoid development. In all cases some lymphoid development proceeds, as assessed by phenotypic markers. In −/− mice, these cells are nonfunctional, even in response to mitogens that do not require Jak3 activation; this suggests a possible spectrum of effects on functional differentiation. The difference in the differentiation of $CD4^+$ versus $CD8^+$ T cells is readily demonstrable, and although the basis of this difference is unknown, it is also seen in γ_c-deficient mice.

Jaks are critical for signaling through cytokine receptors in a variety of lineages. The expression of Jak3 in myeloid cells suggests an importance in these lineages. The phenotype of the −/− mice clearly demonstrates that although Jak3 is critical for normal lymphoid development, it is not required (or is functionally redundant) for myeloid lineages. Therefore, the phenotype of mice that are deficient in other Jaks will be of interest. Because the phenotype of the −/− mice is that of SCID, our results support the hypothesis that mutations of *Jak3* and the absence of Jak3 in humans with SCID are sufficient to account for their immunodeficiency (*12*). Although the extent to which *Jak3* contributes to non–X-linked SCID is not currently known, this deficiency may be an excellent setting for gene therapy. The availability of a mouse model will be of value in verifying this hypothesis and conducting preclinical studies.

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16. We thank X. Y. Zhou and A. d'Azzo for ES cells, C. J. Nagy and J. Swift for technical assistance, F. G. Behm for hematological analysis, K. Yamamoto and O. Silvennoinen for discussions, and J. J. Parobek and J. Zacher for photography. Supported by National Cancer Institute Cancer Center Support (CORE) grant P30 CA21765; National Institute of Diabetes and Digestive and Kidney Diseases grant RO1 DK/HL42932 and National Heart, Lung and Blood Institute grant PO1 HL53749 (J.N.I.); and American Lebanese Syrian Associated Charities.

28 August 1995; accepted 25 September 1995

Superior Parietal Cortex Activation During Spatial Attention Shifts and Visual Feature Conjunction

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Positron emission tomography was used to measure changes in the regional cerebral blood flow of normal people while they searched visual displays for targets defined by color, by motion, or by a conjunction of color and motion. A region in the superior parietal cortex was activated only during the conjunction task, at a location that had previously been shown to be engaged by successive shifts of spatial attention. Correspondingly, the time needed to detect a conjunction target increased with the number of items in the display, which is consistent with the use of a mechanism that successively analyzes each item in the visual field.

A central issue for theories of attention is whether a particular visual object is detected by the simultaneous analysis of all objects across the visual field (parallel search) or by the successive analysis of each object (serial search). To investigate this issue, psychologists have used visual tasks in which people search an array of items for the presence of a prespecified target item (*1*). Depending on conditions, the accuracy and speed shown in detection of a target can be independent of the number of distractor objects in the field (a flat search

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function) or can degrade proportionally with the number of distractors (an increasing search function).

Increasing search functions can result from either a parallel analysis that becomes less efficient as the number of items increases or from the use of a serial attentional mechanism that is successively shifted to items or groups of items at different locations in the field (2). Attempts to decide between these two alternatives have mostly focused on behavioral and computational approaches. An alternative way is to independently identify neural systems involved in spatial shifts of visual attention and assess their activity during tasks yielding flat or increasing search functions.

Several lines of evidence indicate that the parietal cortex is involved in the shifting of attention to different objects or locations in space. Visual responses of single cells in a monkey's posterior parietal cortex have been shown to be modulated by the location of the animal's attention (3). In humans, lesions of the parietal cortex commonly affect the ability to attend to contralateral objects (unilateral neglect) (4). Finally, positron emission tomography (PET) studies have indicated that regions of the superior parietal cortex are activated when people shift attention to different regions of the visual field (5).

In three visual search tasks, study participants saw a display consisting of four square windows containing moving colored dots (Fig. 1). Each window appeared at the vertex of an imaginary square, with a fixation cross at the center of the display. The dots in any window could move at 3° or 10° per second and be colored red-orange or orange. Participants pressed the left of two keys to report the presence of a target or the right key to report its absence. In the "color" condition, all four windows displayed orange dots (target absent), or one randomly chosen window displayed the red-orange dots (target present). The dots in two randomly chosen windows moved at the fast speed, and the dots in the other two windows moved at the slow speed. In the "motion" condition, the dots in all four windows moved at the slow speed (target absent), or the dots in one randomly chosen window moved at the fast speed (target present). The dots in two randomly chosen windows were colored red-orange, and the dots in the other two windows were colored orange. In the "conjunction" condition, participants pressed the left key if one of the windows contained dots that were both red-orange and moved at the fast speed (target present); otherwise, they pressed the right key (target absent) (6).

A group of 17 people performed the color, motion, and conjunction tasks during a series of nine PET regional cerebral blood flow (rCBF) scans with ^{15}O as the tracer (7). Two control conditions were included: a fixation point scan in which only the fixation point was present, and two passive

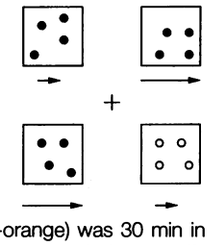

Fig. 1. The stimulus display during a target-present color task trial. Each square window was centered at an eccentricity of 4°, was 2° in length, and contained roughly 40 dots, where each dot (empty circles, orange; filled circles, red-orange) was 30 min in diameter. The arrows under each window specify the two speeds at which the dots could move (3° per second or 10° per second). The direction of dot motion (left or right) varied randomly over trials. During the color task, the two speeds were assigned to two windows each, whereas during the motion task, the target and distractor colors were assigned to two windows each. The luminance of each dot was 30 cd/m², and the luminance of the background was 22 cd/m². Each display was presented for 500 ms, followed by a 1.5-s interval for pressing the response key.

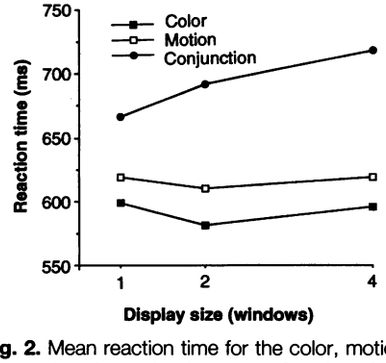

Fig. 2. Mean reaction time for the color, motion, and conjunction tasks shown as a function of display size.

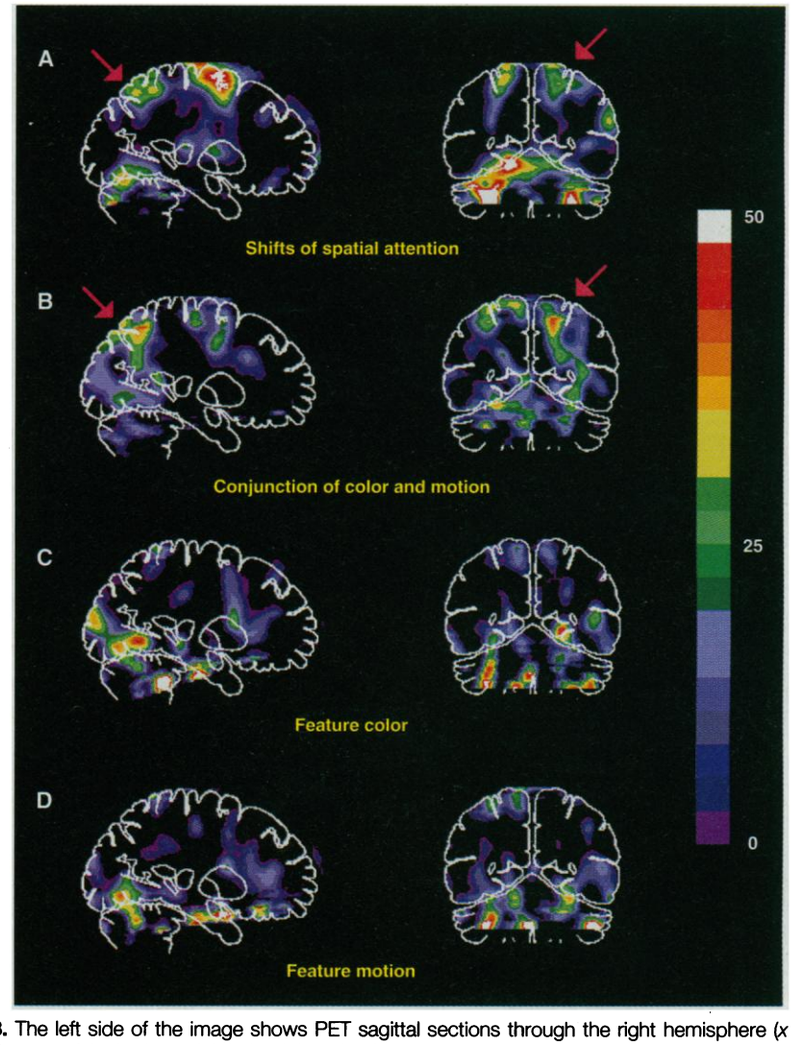

Fig. 3. The left side of the image shows PET sagittal sections through the right hemisphere (x = 18) (anterior part of the brain on right); the right side of the image shows coronal sections through the parietal lobe (y = −59) (left side of the brain on left) in various experimental conditions. The color scale is in normalized PET counts. The red arrows indicate the location of the right superior parietal area that is commonly active during feature conjunction and shifts of spatial attention. (**A**) Shifts of spatial attention. (**B**) Conjunction of color and motion. (**C**) Feature color. (**D**) Feature motion.

scans in which search displays (containing two randomly positioned target and two nontarget color and speed values) were presented but participants did not perform any discriminations and pressed alternate keys on successive trials (8). To determine task-related differences in activity, we subtracted the passive condition from the active conditions, using the image subtractions that yielded the least movement artifact. For an analysis of visual search as a function of set size, participants performed the three tasks in a separate session in which one, two, or four windows appeared during any trial (9).

Performance was worse in the conjunction than in the feature tasks for both reaction times [$F(2,28) = 30.4$, $P < 0.001$] and errors [$F(2,28) = 5.26$, $P < 0.05$]. Search functions were flat for the feature tasks and increasing for the conjunction task (Fig. 2). This difference was reflected in a significant task–by–display-size interaction [$F(4,56) = 4.47$, $P < 0.005$] (*10*).

Functionally, the most pronounced and consistent difference across the entire brain among color, motion, and conjunction conditions was localized in the superior parietal lobe (Fig. 3, B to D; Table 1). Although the conjunction task yielded robust activations in the superior parietal lobe and precuneus, with the strongest activations in the right hemisphere, the color and motion tasks did not produce any activation in the right hemisphere and produced weaker and less reliable activations in the left hemisphere (Table 1) (*11*).

We determined whether these parietal activations corresponded to those that have previously been associated with shifts of spatial attention (*5*). In that experiment, participants detected the onset of small visual stimuli that were presented along a series of predictable positions in the right or left field, with a leftward or rightward direction, while maintaining central fixation. Psychophysical evidence indicated that under those conditions, attention was spatially shifted across the various locations (*12*). The four attention-shifting conditions from the earlier work (right or left visual field, leftward or rightward direction) were averaged (with a fixation condition as control) to yield a composite image, shown in Fig. 3A. The shifting-attention and conjunction images show similar regions of activation in the superior parietal lobule and precuneus in the left and right hemispheres. To quantify this correspondence, the rCBF magnitudes at the parietal locations specified in the shifting-attention image were determined in the conjunction and feature images for each participant (*13*). The mean activation was greater and more consistent (as measured by *t* scores) in the conjunction than in the feature tasks for all superior parietal regions (Table 2). A within-subjects analysis of variance (ANOVA), chosen to minimize anatomical variability, yielded significant results of task [$F(2,14) = 5.68$, $P < 0.05$] for the right posterior focus, with significant contrasts between the conjunction condition and both the color [$F(1,14) = 4.92$, $P < 0.05$] and motion [$F(1,14) = 10.9$, $P < 0.01$] conditions. There was a marginal effect for the right anterior focus [$F(2,14) = 3.35$, $P = 0.065$] and no effect for the left parietal focus (*14*).

The common parietal activations in the attention-shifting and conjunction tasks suggest that serial shifts of spatial attention do occur during tasks that produce increasing search functions. One alternative explanation is that people in the conjunction condition are shifting attention between the color and motion features rather than to different spatial locations. An earlier study, however, found no evidence for superior parietal activation under conditions in which participants divided their attention among the color, form, and motion of visual objects (*15*). A second explanation is that nonselective attentional factors such as arousal, which are related to the greater difficulty of the conjunction task, might selectively activate the superior parietal lobe. This is unlikely, because superior parietal activity has not been observed during the performance of other difficult visual tasks that do not involve spatial shifts of attention (*13*, *15*, *16*).

The present results are therefore more consistent with models that include at some stage of processing a spatial serial mechanism for distinguishing between targets and distractors than they are with models advocating parallel processing across multiple objects and competitive selection (*1*).

Table 1. Coordinates, magnitudes, and *t* scores for all local maxima in the parietal lobe that exceeded 20 PET counts during each task as compared with a passive control task. Activations in the superior parietal lobule (SPL) and precuneus (PC) for the conjunction, motion, and color tasks are shown (R, right; L, left). The *t* scores (*t*) show the consistency of activation across individuals. The corresponding *P* values are not reported because they are not accurate estimators of local statistical significance. Sample size (*n*) varies somewhat with coordinate because not all participants were well sampled at superior brain regions. Coordinates are in millimeters (*x*, *y*, *z*) from a 0, 0, 0 point situated at the midline of the brain (*x*), at the anterior commissure (*y*), and at the level of the anterior and posterior commissure (AC-PC line; *z*) (*7*). The magnitude is in normalized PET counts, which are linearly related to rCBF (*7*).

Area	Coordinates			Magnitude	*t*	*n*
	x	*y*	*z*			
			Conjunction (passive)			
R SPL	33.0	−69.0	50.0	32.0	2.70	10
	31.0	−46.9	54.0	29.9	3.57	10
	22.9	−79.0	46.0	31.7	3.59	11
R SPL-PC	14.9	−71.0	50.1	33.8	6.03	10
	16.9	−59.0	44.1	34.8	4.17	13
L SPL	−27.0	−58.9	55.9	21.8	4.63	7
	−30.9	−53.1	43.9	21.6	2.58	13
L SPL-PC	−11.1	−69.1	50.0	24.3	4.06	10
	−8.9	−53.0	56.2	24.9	3.00	10
			Motion (passive)			
L SPL	−29.1	−55.1	54.0	23.3	3.05	11
L SPL-PC	−9.1	−68.9	51.8	20.4	3.59	9
	−10.9	−55.0	56.0	21.3	3.24	10

Table 2. Magnitude of activity, in normalized PET counts, at superior parietal locations associated with shifts of attention (see Table 1 for details). The *t* scores reflect the consistency of such foci in the conjunction, color, and motion conditions of the experiment reported here. The ANOVA is a one-factor (task) within-subject ($n = 8$) analysis. Cx-Mo and Cx-Co are preplanned contrasts between conjunction (Cx), color (Co), and motion (Mo) conditions at defined locations. NS, not significant.

Area	Coordinates			Magnitude (*t* score)			ANOVA (*F*)	Cx-Mo (*P*)	Cx-Co (*P*)
	x	*y*	*z*	Conjunction	Color	Motion			
R SPL	21	−61	50	21 (2.07)*	−8 (−0.82)	−14 (−1.36)	5.68*	<0.01	<0.05
R SPL	23	−47	52	15 (1.53)	−0.7 (−0.10)	5 (0.52)	3.35	<0.05	NS
L SPL	−17	−59	58	15 (4.12)**	4 (0.49)	12 (1.10)	0.16	NS	NS

*$P < 0.05$. **$P < 0.01$.

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6. In a psychophysical session before the PET session, participants' reaction times for the color and motion tasks were equated, and participants practiced the conjunction task. During the color blocks, the similarity of the target and distractor colors was varied. The distractor color that yielded reaction times most similar to the reaction times in the motion task was chosen for the following PET session.
7. During the PET session, each task was presented twice, with target probabilities of 0.2 and 0.8 in different blocks. These changes in probability were introduced to study the neural systems involved in target detection, but they are not part of this report. PET scans were performed with a PET VI scanning system [M. Yamamoto, D. C. Ficke, M. M. Ter-Pergossian, *IEEE Trans. Nucl. Sci.* **29**, 529 (1982)] and the standard ^{15}O-labeled (half-life, 123 s) water bolus injection technique, which has been previously described [P. Herscovitch, J. Markham, M. E. Raichle, *J. Nucl. Med.* **24**, 782 (1983)]. Scans were 40 s long, which allowed nine scans to be acquired during a single session. Images were obtained from each participant for each experimental condition and were normalized to a common value. For each participant, change images corresponding to specific conditions (see text) were created by subtraction of one image from another. All change images were transformed to a standard stereotactic space [J. Talairach and P. Tournoux, *Co-Planar Stereotaxic Atlas of the Human Brain* (Georg Thieme Verlag, Stuttgart, Germany, 1988); P. T. Fox, J. Perlmutter, M. E. Raichle, *J. Comput. Assisted Tomogr.* **9**, 141 (1985)] and then averaged across participants. The averaged subtraction image was then searched to identify the magnitude and location in stereotactic coordinates of all positive and negative local maxima [P. T. Fox, M. A. Mintun, E. M. Reiman, M. E. Raichle, *J. Cereb. Blood Flow Metab.* **8**, 642 (1988); M. A. Mintun, P. T. Fox, M. E. Raichle, *ibid.* **9**, 96 (1989)].
8. Participants were always instructed to maintain fixation, which was monitored by means of electrooculography. The fixation scan was presented in position 5, and the two passive scans were presented in positions 3 and 7. The color and motion scans were counterbalanced over positions 1, 2, 4, and 6, whereas the two conjunction scans occurred in positions 8 and 9. Although the conjunction conditions were presented after the color and motion conditions, it is unlikely that differences between conditions were caused by this factor. We did not observe any effect of this nature in a similar experiment [D. L. Hunton, M. Corbetta, G. L. Shulman, F. M. Miezin, S. E. Petersen, in preparation] in which task order was balanced. Moreover, there was no difference between the early (scan 3) and late (scan 7) passive conditions.
9. Participants performed three blocks of 66 trials for each task, and target probability was fixed at 0.5.
10. A 2:1 ratio of slopes in the target-absent and target-present conditions is sometimes considered a diagnostic for serial self-terminating search. In the present experiment, the slope in the target-absent condition (9 ms per item) of the conjunction task was actually less than that for the target-present condition (25 ms per item). The relative ease of the target-absent condition may reflect the use of a single distractor value rather than multiple distractor values (*1*). There also appears to have been a criterion shift toward no-target responses, perhaps because of the fixed display duration, with a significant main effect of response [$F(1,14) = 14.9$; $P < 0.005$] in the error data.
11. The activations during the conjunction task for both the left and right superior parietal regions were consistent when either the passive or fixation-point control was used. During the feature tasks, participants showed no activity in the right parietal region when either control condition was used. The left parietal activity during the feature tasks was more variable, with more color-related activity in the fixation-point control and more motion-related activity in the passive control, as reported in Table 1.
12. Participants' reaction time to targets occurring at predicted locations was significantly faster than their reaction time to targets occurring at nonpredicted locations. This advantage in reaction times is typically interpreted as reflecting shifts of attention to the predicted location. Because no stimulation occurred at the predicted location before the shift of attention, these shifts were driven endogenously, as in the conjunction task.
13. Quantitatively, all superior parietal activations with a magnitude greater than 20 counts were selected from the shifting-attention image. This magnitude is based on an estimation of significant responses for different sample sizes. This procedure yielded coordinates from two right hemispheric foci and one left hemispheric focus, which were applied to the present data set. For each participant, a sphere with a radius of 7 mm, based on the spatial resolution of the scanner, was centered on each focus. This sphere was applied separately to the conjunction, color, and motion images, with the passive as control, and the magnitude of activation at each locus was determined. This replication analysis is an unbiased way to test hypotheses about patterns of activation at prespecified brain locations and provides reliable estimates of local probability [see R. L. Buckner *et al.*, *J. Neurosci.* **15**, 12 (1995) for a more complete description of method and rationale].
14. Initially, an ANOVA with task and target probabilities was conducted. Because this analysis yielded no main effect or interaction involving target probability, this factor was collapsed in the one-factor ANOVAs presented in the text. We obtained similar results using all available information in a between-participants design, in which data from some scan pairs for some participants were eliminated due to movement artifacts. A similar feature-conjunction asymmetry at the same right parietal region has been replicated in a recent experiment involving color and orientation perception (*8*).
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17. We thank the reviewers for their helpful suggestions. Supported by NIH grants NS06833, NS2533, and EY08775; ONR grant N00014-89-J-1426; and the McDonnell Center for the Study of Higher Brain Function.

26 April 1995; accepted 4 August 1995

Positional Cloning and Sequence Analysis of the *Drosophila* Clock Gene, *timeless*

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The *Drosophila* genes *timeless* (*tim*) and *period* (*per*) interact, and both are required for production of circadian rhythms. Here the positional cloning and sequencing of *tim* are reported. The *tim* gene encodes a previously uncharacterized protein of 1389 amino acids, and possibly another protein of 1122 amino acids. The arrhythmic mutation tim^{01} is a 64–base pair deletion that truncates TIM to 749 amino acids. Absence of sequence similarity to the PER dimerization motif (PAS) indicates that direct interaction between PER and TIM would require a heterotypic protein association.

Circadian behavioral rhythms, such as human sleep-wake and insect locomotor activity cycles, persist in constant environmental conditions with a period of about a day. Although the phases of such rhythms can be reset by environmental stimuli, particularly light, propagation of the rhythms in the absence of environmental cues indicates action of an endogenous physiological process. Genetic studies of circadian rhythmicity began in earnest with the discovery of clock mutants in *D. melanogaster* (*1*). The mutations affected an X chromosome–linked gene, *per* (*1*, *2*). Recent work has shown that in wild-type flies *per* is expressed with a circadian rhythm, in which peak levels of *per* mRNA are observed near the end of the day (*3*, *4*). *per* mutations that abolish or alter the period length of behavioral rhythms produce parallel effects on the *per* transcript rhythm (*3*, *4*). The PER protein is predominantly nuclear (*5*–*7*) and also accumulates with a circadian rhythm (*5*, *6*, *8*, *9*). However, PER is most abundant late at night when *per* RNA levels are low (*5*, *8*, *9*, *10*). These observations, and the finding that constitutive overexpression of PER protein can substantially diminish the *per* mRNA rhythm in certain cells of the fly (*10*), are consistent with the proposal that PER negatively regulates expression of its own mRNA (*3*). Such feedback control may be indirect, because PER lacks a known DNA binding motif (*11*).

PER contains a sequence with homology to a domain (PAS) found in three basic helix-loop-helix (bHLH) transcription factors (*12*, *13*). The PAS domain of PER can support dimerization, or alternatively, intramolecular binding to a nonhomologous sequence located on the COOH-terminal side of the PAS domain (*14*, *15*). Two proteins containing PAS, AHR and ARNT, also interact to form the activated aryl hydrocarbon receptor (*13*, *16*). These

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