certainly is important, but it's not the whole story. Endogenous SNX1 is enriched on highly curved tubular profiles that emerge from the PtdIns3P-enriched endosome. To achieve such targeting SNX1 employs a combination of binding domains; its PX domain binds PtdIns3P, whilst another domain, a Bin/Amphiphysin/Rvs (BAR) domain, binds to highly curved membranes. By combining these modules, SNX1 can correctly localise to a sub-domain of the endosome. Interestingly, the BAR domain of SNX1 can do more than just sense curvature; it can actually impose curvature upon membranes, deforming liposomes into highly curved membrane tubules, possibly assisting in the generation of transport intermediates.

How can BAR domains sense membrane curvature? Well, BAR domains form a banana-shaped dimer that is positively charged upon its concave face. *In vitro*, this domain binds preferentially to liposomes with high intrinsic curvature, suggestive of an ability to 'sense' curvature, and can even turn these liposomes into lipid tubes, an attribute thought to represent an ability to deform membranes.

Do other SNXs contain BAR domains? Yes — a sub-group of nine proteins has recently been described, the SNX-BAR proteins, based upon the presence of predicted BAR domains. However, only SNX1 has so far been shown to contain a functional BAR domain. Defining the characteristics of these other BAR domains containing SNXs will be of great interest.

Are all SNXs targeted to endosomes? Surprisingly, no. Whilst it is true that many are associated with this organelle, growing evidence suggests that SNXs may control membrane trafficking at other compartments. For example, the PX domain of SNX4 binds PtdIns3P and PtdIns3,4P_2, allowing SNX4 to shuttle between endosomes and the PtdIns3,4P_2-enriched plasma membrane. The PX domain of SNX9 binds a range of phosphoinositides present at the plasma membrane. SNX9 itself localises to the plasma membrane and is required for clathrin-mediated endocytosis. So, SNXs can act at a range of membranes, apparently dictated by the phosphoinositide-binding capability of their SNX-PX domain.

Do SNXs have any other function? SNXs have been viewed as regulators of cargo sorting; however, their domain architecture suggests that some may integrate into other cellular processes. In yeast, Snx4p (also known as Cvt13p) also regulates cytoplasm-to-vacuole targeting, and in mammalian cells SNX23 is identical to a kinesin (KIF16b) that has recently been shown to regulate endosome motility upon microtubules, so SNX functions need not be restricted to cargo sorting. Three mammalian SNXs contain regulator of G-protein signalling (RGS) domains; in the case of SNX13, this domain allows it to modulate $G_{\alpha s}$-signalling. Interestingly, SNX13's interaction with $G_{\alpha s}$ also allows it to enhance degradative sorting of the EGFR, suggesting that SNX13 functions as a node between signalling and sorting; an exciting concept for purveyors of both fields! With the finding that other SNXs contain RGS domains, Ras-association domains, SH3 domains or PDZ domains, an intriguing hypothesis is that these proteins may well regulate, or be regulated by, signalling cascades determined by the activation state of the cell.

Where can I find out more?

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BAR domains - Harvey McMahon's website: http://www2.mrc-lmb.cam.ac.uk/NB/McMahon_H/group/

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The chordate ParaHox cluster

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The ParaHox gene cluster is an evolutionary sister to the Hox cluster, which is involved in patterning the anterior–posterior axis of animals. First discovered in the cephalochordate amphioxus (*Branchiostoma floridae*) [1], the ParaHox gene cluster is thought to have arisen by duplication of an ancestral homeobox gene cluster that produced the ParaHox and Hox clusters, respectively [1,2]. While the Hox cluster is widely conserved among animals, ParaHox clusters are only known from some chordates [1,3]. The detailed organisation of these clusters has not been examined. The amphioxus ParaHox cluster contains three homeobox genes, *AmphiGsx*, *AmphiXlox* and *AmphiCdx*. These genes are expressed along the anterior–posterior axis of amphioxus in the central nervous system and gut, in a fashion that is colinear with their order along the chromosome [1]. To gain a deeper understanding of the ParaHox cluster we have sequenced over 100 kb encompassing the complete cluster of amphioxus. Comparing this sequence to the orthologous regions in the genomes of mice and humans reveals that these clusters are not merely an association of three genes, but exhibit a higher order of conservation and maintain the overall organisation, relative gene size and spacing. Furthermore, we show that the mammalian ParaHox cluster is the single remnant of four ancestral clusters.

Sequencing of the amphioxus ParaHox cluster has confirmed that it contains only three homeobox genes. We have deduced the complete coding sequence for all of these genes (see Supplemental Data published

with this article online). *AmphiGsx* codes for a 248 amino acid protein that is orthologous to vertebrate Gsh1 and Gsh2. *AmphiXlox* encodes a 313 amino acid protein with the same domain structure as its vertebrate orthologues, such as human IPF1; this indicates that the Xlox domain structure was ancestral for the chordates. The 304 amino acid AmphiCdx protein is the sister group to the vertebrate Cdx groups in phylogenetic trees, and similarly the AmphiGsx sequence is a sister group to the vertebrate Gsh1/2 groups (see Supplemental Data). This implies that the duplications that gave rise to the vertebrate Gsh1/2, and similarly the various vertebrate *Cdx* genes, occurred after the divergence of the amphioxus and vertebrate lineages, presumably during the genome-wide duplications at the origin of the vertebrates [4].

It has previously been hypothesised that there is a ParaHox cluster on human chromosome 13 and mouse chromosome 5 [1], but the precise organisation of these mammalian clusters has not been examined. The mammalian ParaHox cluster is two to three times larger than that of amphioxus, but the relative spacing of genes (i.e. *Gsx* to *Xlox*, and *Xlox* to *Cdx*) is strikingly similar (Figure 1 and Supplemental Data). Intriguingly, the relative spacing between Hox genes is also generally conserved within the chordates [5]. Mammalian Hox genes are controlled by chromatin modulation and long-range enhancers, both of which are affected by distance [6,7]. How the ParaHox cluster is regulated remains to be resolved, but the conservation of relative spacing across chordate ParaHox clusters is consistent with a constraint on their transcriptional regulation.

The conservation of gene size and spacing is all the more significant as the mammalian ParaHox clusters contain many repetitive and transposable elements. These elements provide ample opportunity for genomic rearrangements to occur, but such alterations have clearly been constrained and ParaHox cluster organisation conserved.

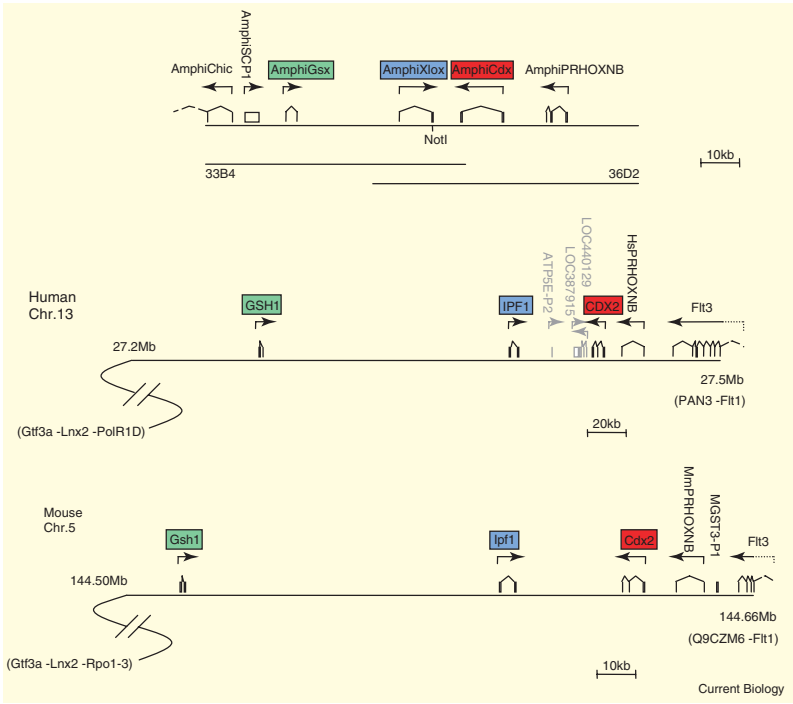

Figure 1. Chordate ParaHox clusters.

The amphioxus ParaHox gene cluster (top) compared to the clusters of humans and mice. The amphioxus cluster is encompassed by two PAC clones, 33B4 and 36D2 (Genbank accessions AC129948, AC129947). The ParaHox genes are highlighted in colour, and the three predicted ORFs between human IPF1 and CDX2 are shown in grey to denote that they are probably non-coding (see Supplemental Data). Arrows show transcriptional orientation, and further flanking genes in the mammalian genomes are shown in brackets. All three clusters are drawn to scale so that the conserved organisation of the clusters can be seen.

Apart from the Hox genes, vertebrate Hox clusters do not contain any other genes. The same holds true for the ParaHox cluster — no other genes are identified within the chordate ParaHox clusters besides *Gsx*, *Xlox* and *Cdx* (see Supplemental Data).

We have sequenced an additional 20 kb 5′ of *AmphiGsx*, and a further 34 kb 5′ of *AmphiCdx*. These sequences include the non-homeobox genes neighbouring the cluster and allow us to reconstruct the arrangement in the chordate ancestor. Furthermore they reveal that chromosomal rearrangements have happened almost immediately outside the single remaining mammalian ParaHox cluster, but not within it.

The ParaHox cluster of the chordate ancestor was flanked by *CHIC* and *PRHOXNB* genes. Amphioxus has retained this ancestral organisation. Along the mammalian lineage, the ParaHox cluster duplicated to four copies. These duplications were followed by gene loss from the four vertebrate paralogy regions, including loss of ParaHox genes so that only a single ParaHox cluster remains in mammals. Genomic reorganisations have occurred adjacent to the single ParaHox cluster of mammals, but not within it (Figure 2). This tight maintenance of a single ParaHox cluster in mammals, orthologous to that of amphioxus, probably reflects an evolutionary constraint to maintain the cluster, which could be due to a conserved mode of gene regulation. Such a strong evolutionary constraint on the cluster is also reflected by the conservation of relative gene sizes and spacing.

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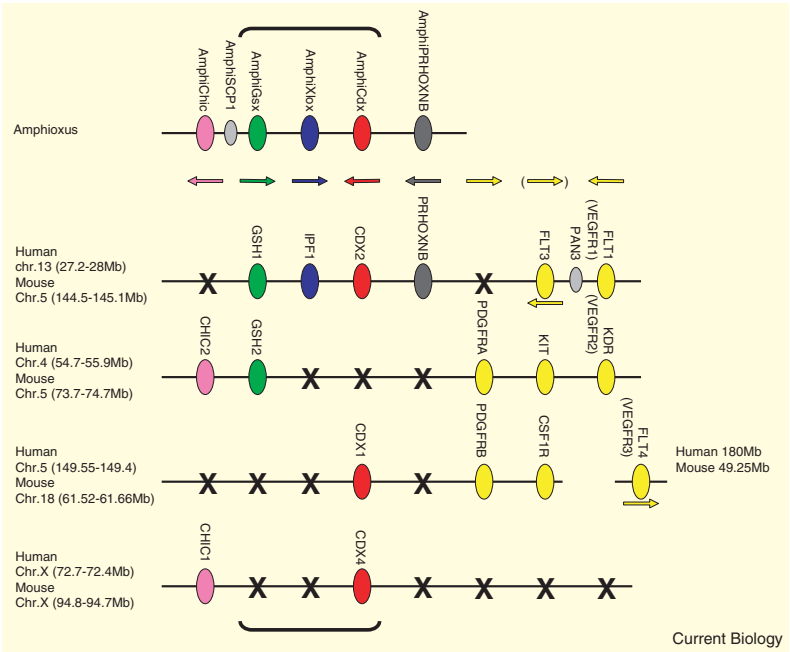

Figure 2. Maintenance of ParaHox clusters.

Schematic of the amphioxus ParaHox cluster (top), with flanking genes, and the mammalian ParaHox clusters with the mammalian ParaHox paralogy regions. The amphioxus cluster has retained the organisation present in the chordate ancestor. Arrows denote transcriptional orientation, which has been conserved between the ParaHox clusters and the paralogy regions. The pattern of gene linkage and orientation indicates that the mammalian genomic regions arose from duplications of the entire region, followed by extensive gene loss (indicated by 'X'). Only a single intact ParaHox cluster remains in mammals, and genomic rearrangements have occurred up to its edges, but not within it. Each column of receptor tyrosine kinase genes (yellow) is a distinct paralogy group (i.e. PDGFRA is a paralogue of PDGFRB). FLT4 has been transposed to a different location on the chromosome, and the orientation of FLT3 is the reverse of that of its paralogues KIT and CSF1R, the orientation of KIT and CSF1R presumably being the same as the ancestral organisation. AmphiSCP1 is reduced to indicate the possibility that it is a retrotransposition (see Supplemental Data). Mammalian PAN3 is reduced because it is not a receptor tyrosine kinase gene and hence is not analysed here.

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Supplemental data

Supplemental data including experimental procedures are available at http://www.current-biology.com/cgi/content/full/15/20/R820/DC1/

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Weak suppression of visual context in chronic schizophrenia

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Several theories propose that diverse cognitive deficits associated with schizophrenia are attributable to an impaired ability to use information (context) to interpret stimuli [1–3]. We asked how such a deficit might influence vision, a modality that depends heavily on low-level contextual processing — for example, 90% of cells in primary visual cortex, V1, are subject to suppression by their neighbours [4].

Recent evidence suggests that some contextual interactions in vision may be weaker in schizophrenia. Must *et al.* [5] reported that, in schizophrenic observers, the detection of an oriented target is less facilitated by the presence of collinear 'flanks' than usual. It is unclear, however, whether this reduced performance level arises from impaired lateral connectivity in V1, as the authors conclude, or is the result of other cognitive deficits associated with schizophrenia.

To differentiate these possibilities we require a task for which reduced contextual interactions actually improve performance. Against a backdrop of generalised cognitive impairment, tasks at which schizophrenic observers excel are both rare and revealing: enhanced performance cannot be attributed to general factors and serves to illuminate the condition's underlying neural mechanism [6].

Figure 1A illustrates how contextual suppression can influence normal visual perception by causing the ringed target to appear lower contrast when presented within a high-contrast surround than in isolation [7]. Convergent data from psychophysics and functional magnetic resonance imaging