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Supplementary Information accompanies the paper on **www.nature.com/nature**.

Acknowledgements C.D.B. and K.B. collected the data, whereas T.N.S. helped design the experiments and developed the computer program. We thank F. Batiste, A. Rashed, G. Ruxton, M. Speed, H. Van Gossum and D. Wilkinson for comments on our manuscript. The research was approved by the Carleton University Research Ethics Committee and conducted according to the guidelines set out in the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans. The work was supported by grants to T.N.S. from NSERC, the Canada Foundation for Innovation and the Ontario Innovation Trust.

Competing interests statement The authors declare that they have no competing financial interests.

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Hox cluster disintegration with persistent anteroposterior order of expression in *Oikopleura dioica*

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Tunicate embryos and larvae have small cell numbers and simple anatomical features in comparison with other chordates, including vertebrates. Although they branch near the base of chordate phylogenetic trees[1], their degree of divergence from the common chordate ancestor remains difficult to evaluate. Here we show that the tunicate *Oikopleura dioica* has a complement of nine *Hox* genes in which all central genes are lacking but a full vertebrate-like set of posterior genes is present. In contrast to all bilaterians studied so far, *Hox* genes are not clustered in the *Oikopleura* genome. Their expression occurs mostly in the tail, with some tissue preference, and a strong partition of expression domains in the nerve cord, in the notochord and in the muscle. In each tissue of the tail, the anteroposterior order of *Hox* gene expression evokes spatial collinearity, with several alterations. We propose a relationship between the *Hox* cluster breakdown, the separation of *Hox* expression domains, and a transition to a determinative mode of development.

Hox genes are involved in establishing morphological identities along the anteroposterior axis of bilaterians and cnidarians[2]. Phylogenetic analysis suggests that the ancestor of all bilaterians had at least seven *Hox* genes—five anterior, one central and one posterior, according to the nomenclature of ref. 3—grouped in a genomic cluster where the gene order correlated with sequential expression along the anteroposterior axis. Both *Hox* gene sequences and the *Hox* cluster evolved in distinct animal lineages, with occasional cluster splits in invertebrate protostomes (*Drosophila*, *Caenorhabditis*), and gene losses[4,5]. The significance of these discrete alterations in terms of developmental changes is a challenging enigma. Major gains of *Hox* genes coincided with the evolution of chordates, including the multiplication of entire clusters in vertebrates and an increment in the number of posterior paralogues up to six in vertebrates and cephalochordates[6–8]. Recent sequencing in the tunicate ascidian *Ciona intestinalis*[9,10] revealed only three posterior genes, which might equally represent a gain or a loss of genes. *C. intestinalis* also has only one central gene, probably reflecting a secondary loss of two genes, and its *Hox* cluster is split into five segments.

To gain further insight into the evolution of tunicate *Hox* complements, we identified the *Hox* genes of *O. dioica* and studied their expression and genomic organization. *O. dioica* belongs to the appendicularians, one of the three classes of tunicates. We recently showed that *O. dioica* has a very small (60–70 megabases), compact genome (one gene every 4 kilobases (kb))[11]. Unlike ascidians, appendicularians conserve a chordate tail complex during the entire short life cycle (4 days at 20 °C in *O. dioica*). PCR cloning with degenerate primers, and whole-genome shotgun sequencing of both outbred and inbred populations (Supplementary Fig. S1), revealed nine candidate *Hox* genes. Full-length complementary DNA species were cloned for each of them, and phylogenetic analyses indicated that *Oikopleura* has three anterior *Hox* genes (*Hox1*, *Hox2* and *Hox4*) and six posterior *Hox* genes (*Hox9A*, *Hox9B*, *Hox10*, *Hox11*, *Hox12* and *Hox13*) (Fig. 1). Therefore, *O. dioica* and *C. intestinalis* share the same number of *Hox* genes but have markedly different *Hox* complements. O. *dioica* has lost the *Hox3* paralogue and all central genes, whereas *C. intestinalis* has probably lost some central genes. Either the posterior genes have been independently amplified in the *Oikopleura* lineage or a chordate ancestor already had a full complement of posterior *Hox* genes, which was subsequently reduced in the *Ciona* lineage.

We studied the expression pattern of each *O. dioica Hox* gene by *in situ* hybridization (see Methods) at 2.5 h after fertilization (tailbud stage), at 4 h (hatched tadpole) and at 6 h (mid-organogenesis). Here, we focus on the 4-h expression patterns (Fig. 2a), which were essentially identical to those seen at 2.5 h and were mostly concentrated in the tail. During late organogenesis, expression patterns evolve further and gradually include additional regions in the trunk/head. The tadpole tail consists of an epidermis, the 20 cells of a notochord, two rows of eight round muscle cells located dorsally and ventrally, and a nerve cord (about 60 neurons and support cells) placed on the left side of the notochord. Taken together, the expression patterns showed similarities to and important differences from those of other animals (Fig. 2b). Each tissue was the site of expression of only a subset of the nine *Hox* genes. Conversely, each *Hox* gene was expressed in only a subset of the four tail tissues, and in extreme cases in a single cell. Overall, the expression domains of distinct *Hox* genes overlapped only weakly, except in the epidermis, and most hybridizing cells expressed a single *Hox* gene. Within this partitioned expression, the sites of expression along the anteroposterior axis showed correlation with the order of the *Hox* paralogues. There were, however, several deviations from the expression collinearity, as defined by a perfect order of the anterior expression limits (with *Hox2* as the classical exception in vertebrates and in

the amphioxus). In a total of 28 two-by-two comparisons of anterior expression limits of *Hox* genes in the four tissues, the anteroposterior order of paralogues is respected in at least 24 cases.

We performed a detailed study of the *Hox* genomic organization by screening a bacterial artificial chromosome (BAC) library with nine distinct *Hox* cDNA probes. Strikingly, none of a total of 156 positive BAC clones hybridized with more than a single *Hox* probe, indicating large distances between distinct *Hox* genes. Genomic walking on about 250 kb on each side of eight *Hox* genes failed to detect linkage between any *Hox* genes, whereas three other homeobox genes were attained (Fig. 3a). The *Hox* genes are therefore more dispersed in the very compact genome of *O. dioica* than are the *Hox* genes of any other animal examined thus far. To describe the genomic environment of each *Hox* gene, we fully sequenced and annotated seven BAC inserts, each containing a different *Hox* gene. Each *Hox* gene was indeed isolated and surrounded by many unrelated genes, at the usual high gene density (Fig. 3b). Because recent reports have shown a partial compartmentalization of animal genomes in large chromatin domains[12,13], we used cDNA cloning and *in situ* hybridization to examine whether the expression of *Hox* genes and their immediate neighbours might be co-regulated.

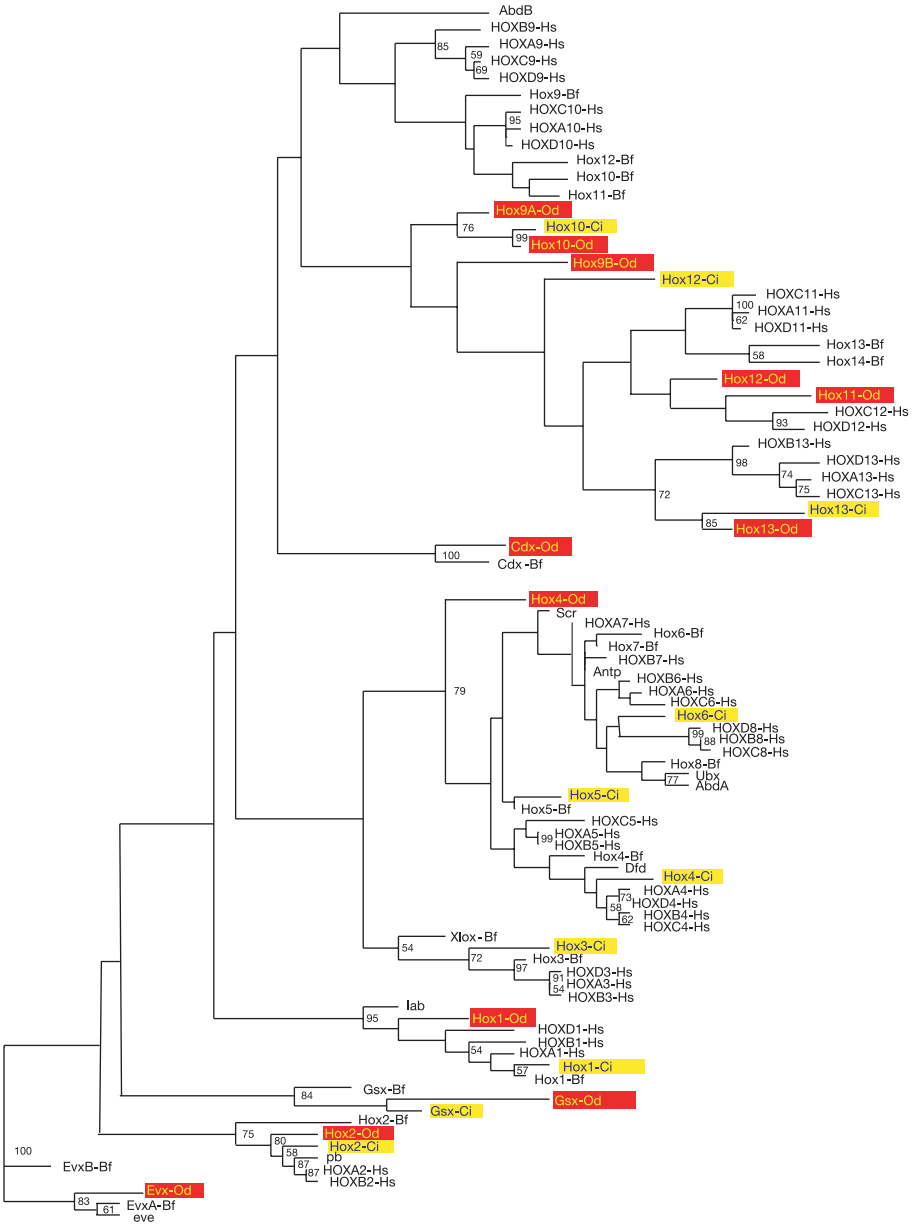

Figure 1 Evolutionary relationship of the *Hox* and *ParaHox* homeodomain sequences inferred by the neighbour-joining method. The neighbour-joining tree including a 1000 replicate bootstrap was inferred by PAUP[26]. *O. dioica* and *C. intestinalis* gene names are highlighted in red and yellow, respectively. These include the *Oikopleura ParaHox* genes *Gsx* and *Cdx* and its unique *Evx* gene, for which genomic and cDNA sequences have been isolated. Other genes are from human (Hs), amphioxus (Bf) and *D. melanogaster*. The same data set was used for maximum-parsimony (MP; PAUP) and quartet-puzzling-likelihood (QP; TREE-PUZZLE[27]) analyses (not shown), leading to the same overall topology. MP and QP methods placed the *O. dioica Hox4* gene together with the other *Hox4* sequences as a monophyletic group.

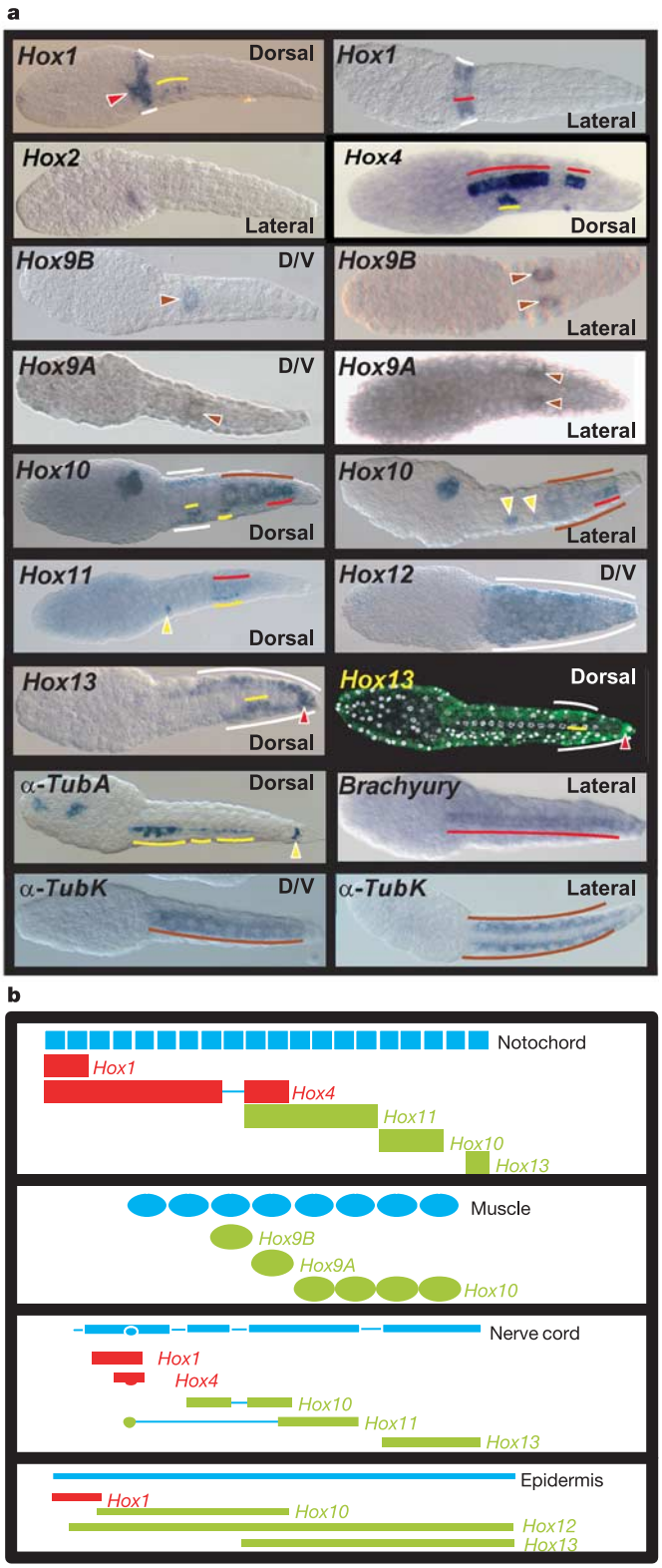

Figure 2 Expression patterns of *Oikopleura Hox* genes at 4 h after fertilization. **a**, The sites of *Hox* gene expression were identified by detection with both alkaline phosphatase and tyramide signal amplification (for confocal microscopy) and through comparisons with signals obtained with three marker genes (*α-tubulin A* (*α-TubA*) for neurons, *α-tubulin K* (*α-TubK*) for muscle cells, and *Brachyury* for notochord[28]). The expression domains are identified with coloured bars or arrowheads (epidermis in white, notochord in red, nerve cord in yellow, and muscle cells in brown). **b**, The schematic organization of each tissue is drawn in blue, from the posterior end of the trunk (left) to the tail tip (right). *Hox* gene expression domains are represented in red for anterior genes and in green for posterior genes. The ISH protocol was adapted from ref. 25.

Almost all expression patterns of *Hox* gene neighbours were ubiquitous (not shown), ruling out local co-regulation and the possibility of an 'attraction' of *Hox* genes to specific chromatin domains. Whereas it is certain that the *Hox* cluster splits of both *C. elegans* and drosophilids were independent events, it is possible that the last common ancestor of *C. intestinalis* and *O. dioica* already had a split cluster. This question remains unanswered because we found no evidence of syntenic conservation in the *Hox* gene environments of either species. Furthermore, the expression patterns of *C. intestinalis Hox* genes are at present limited to three genes[14–16], two of which do not exist in *Oikopleura*, so that the conservation of expression between both tunicates could not be evaluated.

How can these results contribute to our vision of the evolution of tunicate development in chordates? First, the presence of six posterior genes in *Oikopleura* (as opposed to three in *Ciona*) indicates that posterior genes might have been amplified only once and before the radiation of chordates (Fig. 4). If this amplification is correlated with the evolution of the tail, our results are consistent with a single origin of the chordate tail, a question that has remained open until recent times[17,18]. Second, losses of *Hox* clustering and central *Hox* genes—partial in *Ciona* and total in *Oikopleura*—are unique to tunicates among the chordates (Fig. 4). It has been proposed that the *Hox* cluster is ultimately required for the coordination of *Hox* expression timing[19], and its integrity is indeed crucial for a proper expression schedule in the mouse[20]. Moreover, the three species with a split *Hox* cluster (*Ciona*, *Drosophila*, *C. elegans*) do not display temporal collinearity, which is perhaps associated with their fast early development[19]. Similarly, several anterior and posterior *Hox* genes of *Oikopleura* are already expressed at 90 min after fertilization (not shown). Thus, a loss of *Hox* clustering could have facilitated a breakdown of temporal collinearity. If so, however, it is unlikely to be simple cause and effect because the loss of *Hox* clustering ranges from a single cluster split in *D. melanogaster* to a total disintegration in *Oikopleura*. Another possible cause of breakdown of the *Hox* cluster could be the loss of *Hox* gene function, which would relax the constraints for their coregulation: a conservation of function in axis patterning cannot be excluded in *Oikopleura*, considering the anteroposterior order of expression domains. Alternatively, the deviations from strict collinearity might reflect a reallocation of *Hox* genes to later functions, even though spatial regulation properties have surprisingly persisted. In any situation, it is noteworthy that *Hox* genes that lost their function in *C. elegans* and in *D. melanogaster* have remained tightly linked to at least another *Hox* gene, and the loss of *Hox* function therefore does not necessarily induce the *Hox* cluster breakdown.

Striking features of *Hox* expression domains in *Oikopleura* are their weak degree of overlap and a certain degree of tissue preference including strict tissue and cell specificity for three genes (*Hox9A*, *Hox9B* and *Hox12*). The complexity of *Hox* expression patterns supports the notion that the tail, despite its very small cell number and apparently simple anatomy, develops from fairly diverse genetic programmes that could allow the evolution of sophisticated tail functions (for example, pumping water or food, expansion of the house, swimming, or escape response). In a classical hypothesis based on comparisons of crustaceans with insects, a reduction of *Hox* expression overlaps is related to increased regional specialization[21]. However, the generalization of such a relationship encounters several obstacles, not the least of which is the vertebrate embryo axis, along which a rich *Hox* code establishes numerous positional identities within highly overlapping expression domains[22]. A hypothesis in favour of the loss of *Hox* genes in *C. elegans* is the change to determinative development[23,24], which rendered the patterning of the formed anteroposterior axis superfluous, or perhaps even undesirable. A parallel can be drawn with tunicates, because at least ascidians also have a lineage-driven mode of

development. It might be that the role of *Hox* genes in the specification of anterior–posterior position decreased, their role in the specification of tissue type increased, and a separation of expression domains occurred. The *Hox* cluster might have been disorganized to facilitate or permit the separation of expression domains. The expression has become promoter-dependent, and a partial conservation of the promoters could explain why an apparent collinearity remains. □

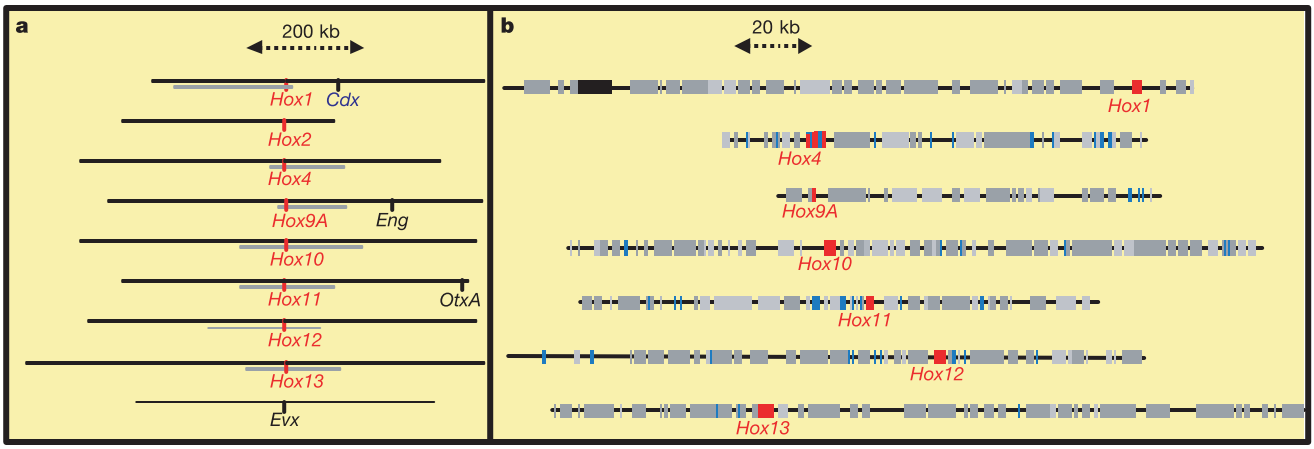

Figure 3 Genomic organization of the *Oikopleura Hox* genes, indicating total *Hox* cluster breakdown. **a**, A sperm BAC library (15×–20× coverage) was screened at high stringency with all nine *Hox* cDNA probes labelled with digoxigenin, and also with a cDNA probe of *Evx*. The inserts of two positive BAC clones were end-sequenced for a genomic walk (black lines). One of each *Hox*-containing BAC clone (grey lines) was fully sequenced. The *Hox2* clone could not be consistently assembled, but included no other *Hox* gene. **b**, The sequence of each BAC clone was annotated using BLASTX (dark grey rectangles) and other gene prediction tools (light grey rectangles)[11]. Each *Hox* gene was isolated in its BAC insert except *Hox4*, which was partly duplicated (see Supplementary Fig. S2). Blue bars represent short repeats conserved within or between BAC clones. A single transposable element related to *Gypsy* elements was identified in the *Hox1* BAC (black rectangle).

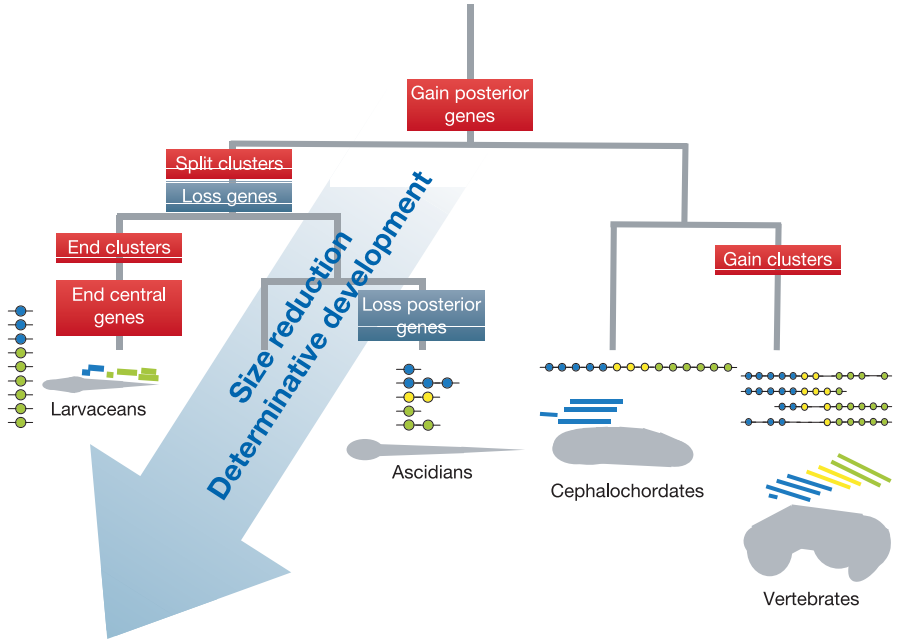

Figure 4 Discrete changes of Hox gene complements in chordates. The chordate ancestor gained a rich set of posterior genes, which were inherited in the three subphyla but partly lost in ascidians. Central genes were gradually lost in tunicates, with larvaceans keeping anterior and posterior genes only. Whereas the *Hox* cluster was multiplied in vertebrates (with subsequent losses of a few paralogues in some clusters), the cluster degenerated in tunicates, and ultimately disappeared in larvaceans. The loss of central genes and of the *Hox* cluster coincides with a partition of *Hox* expression domains, which largely overlap in cephalochordates and vertebrates (ascidian data are still lacking). The motor of both events might be the decrease in size and transition to determinative development.

Methods

Whole-mount *in situ* hybridization

The ISH protocol was adapted from ref. 25 with the following modifications: embryos were fixed overnight in 4% paraformaldehyde in 0.1 M MOPS pH 7.5, 0.5 M NaCl at 4 °C, washed in 0.05 M Tris-HCl pH 8, treated for 1 min with 10 $\mu g\,ml^{-1}$ proteinase K in 0.05 M Tris-HCl pH 8 at 37 °C, followed by incubation in 1 M MOPS, 0.5 M NaCl, 0.1% Triton X-100 at 20 °C for 20 min. Embryos were prehybridized for 1 h and hybridized overnight in 50% deionized formamide, 5 × SSC, 1% blocking reagent at 60 °C. After the washing procedure, the hybridized embryos were blocked in 1% blocking reagent (Roche) and 1% filtered (0.45 μm pore size) lamb sera (Gibco) in PBS for 1 h at 20 °C. They were then incubated for a further 1 h at 20 °C in alkaline-phosphatase-coupled anti-digoxigenin Fab fragments (Roche) and in 1 × PBS, 0.1% Triton X-100 and treated for standard detection as described by Roche. Alternatively, the embryos were incubated in horseradish-peroxidase-conjugated anti-digoxigenin Pod fragments (Roche) for 4 h at 20 °C, followed by 1–4 days of incubation at 20 °C with the Tyramide Signal Amplification kit (Perkin Elmer) for fluorescence staining. Nuclear staining was obtained by incubation overnight at 4 °C with To-Pro-3 iodide (Molecular Probes). Specimens were mounted in Vectashield mounting medium (Vector Laboratories) and analysed with a Leica TCS laser scanning confocal microscope.

Received 13 March; accepted 3 June 2004; doi:10.1038/nature02709.

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Supplementary Information accompanies the paper on **www.nature.com/nature**.

Acknowledgements We thank A. Adoutte for advice throughout the course of this work; R. Aasland, M. Schartl, T. Stach and E. Thompson for their comments at several stages of manuscript preparation; and the personnel of the *Oikopleura* culture facility for technical support. Funding was provided by the Research Council of Norway and the University of Bergen in the frame of the Sars Centre – EMBL partnership contract.

Competing interests statement The authors declare that they have no competing financial interests.

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Biological abnormality of impaired reading is constrained by culture

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Developmental dyslexia is characterized by a severe reading problem in people who have normal intelligence and schooling[1–3]. Impaired reading of alphabetic scripts is associated with dysfunction of left temporoparietal brain regions[2–5]. These regions perform phonemic analysis and conversion of written symbols to phonological units of speech (grapheme-to-phoneme conversion); two central cognitive processes that mediate reading acquisition[6–7]. Furthermore, it has been assumed that, in contrast to cultural diversities, dyslexia in different languages has a universal biological origin[1,8]. Here we show using functional magnetic resonance imaging with reading-impaired Chinese children and associated controls, that functional disruption of the left middle frontal gyrus is associated with impaired reading of the Chinese language (a logographic rather than alphabetic writing system). Reading impairment in Chinese is manifested by two deficits: one relating to the conversion of graphic form (orthography) to syllable, and the other concerning orthography-to-semantics mapping. Both of these processes are critically mediated by the left middle frontal gyrus, which functions as a centre for fluent Chinese reading[9–11] that coordinates and integrates various information about written characters in verbal and spatial working memory. This finding provides an insight into the fundamental pathophysiology of dyslexia by suggesting that rather than having a universal origin, the biological abnormality of impaired reading is dependent on culture.

Unlike alphabetic writing systems that follow a design principle of mapping graphemes (visual form) onto phonemes (minimal phonological units of speech), the Chinese logographic system maps graphic forms (characters) onto morphemes (meanings). The phonology of written Chinese is defined at the monosyllabic level, with no parts of a character corresponding to phonemes. For instance, in the English word 'beech' the 'b' corresponds to /b/, and the latter is a segment of the word. However, the Chinese character 理 is pronounced /li3/ (meaning 'reason', where the numeral refers to Chinese tone), and its phonetic component 里, located on the right (also pronounced /li3/, meaning 'inside'), does not correspond to a piece of the word's phonological form. Hence, Chinese writing does not allow the segmental analysis that is fundamental to