Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Genetics & Development

Functional and ecological impacts of horizontal gene transfer in eukaryotes

Patrick J Keeling

Horizontal gene transfer (HGT) is known to have contributed to the content of eukaryotic genomes, but the direct effects of HGT on eukaryotic evolution are more obscure because many of the best supported cases involve a new gene replacing a functionally similar homologue. Here, several cases of HGT conferring a plausible adaptive advantage are reviewed to examine emerging trends in such transfer events. In particular, HGT seems to play an important role in adaptation to parasitism and pathogenesis, as well as to other specific environmental conditions such as anaerobiosis or nitrogen and iron limitation in marine environments. Most, but not all, of the functionally significant HGT to eukaryotes comes from bacteria, in part due to chance, but probably also because bacteria have greater metabolic diversity to offer.

Address
Canadian Institute for Advanced Research, Botany Department, University of British Columbia, 3529-6270 University Boulevard, Vancouver, BC V6T 1Z4, Canada

Corresponding author: Keeling, Patrick J (pkeeling@interchange.ubc.ca)

Current Opinion in Genetics & Development 2009, **19**:613–619

This review comes from a themed issue on
Genomes and evolution
Edited by Martha Bulyk and Michael Levine

Available online 10th November 2009

0959-437X/$ – see front matter

DOI 10.1016/j.gde.2009.10.001

Introduction: the impact of horizontal gene transfer on eukaryotic evolution

Horizontal or lateral gene transfer (HGT) is the non-sexual movement of genetic information between two organisms. This process was originally recognized from the rapid emergence of drug resistance in *Shigella* strains during outbreaks of dysentery in Japan [1]. A greater appreciation for a more general impact of HGT began with comparative genomics, which revealed so many bacterial and archaebacterial genes derived from HGT that the basic model of tree-like evolution was challenged for these lineages [2–4].

Nuclear genomes are, however, very different from those of prokaryotes, so it is reasonable to ask, is the same true of eukaryotes? Their greater size has made this question difficult to address, because of the significant lag in nuclear genomics has until recently denied us the breadth of sampling required to recognize some kinds of HGT. At the same time, certain aspects of eukaryotic reproduction and evolution will disfavour HGT in the best-studied lineages: in particular, the separation of germ and soma represents a tremendous hurdle in the fixation of foreign genes in a population. As a result, strongly supported cases of HGT are rare in well-studied lineages such as animals (Box 1). Nevertheless, numerous individual cases of HGT have emerged in a wide variety of eukaryotic lineages, and patterns generated by this process have also begun to emerge [5,6,7••].

In general, the impact of HGT across eukaryotes has been uneven: many microbial eukaryotes and plant mitochondria are rich in examples of HGT [6,8–13], whilst other lineages appear to be relatively immune to acquiring new genes. At the same time, some genes are commonly transferred, whilst others are more static. The variable suseceptibility of different genes to HGT was long ago predicted based on how tightly its product was integrated into protein interaction networks [14], but lately even genes for 'core' processes through to be most difficult to exchange have been proposed: for example, translation elongation factors [15,16], and ribosomal RNA [17], although the latter has yet to be shown to be functional.

Another emerging pattern is that most HGT to eukaryotes involves genes from bacteria. In all likelihood, this is partly due to sampling, and partly due to ecological factors [7••]. There are several ways to detect HGT, but the gold-standard is a phylogeny that does not match our expectations (Box 2). Because bacterial genomes are so well sampled and their genes so distantly related to eukaryotic homologues, bacteria-to-eukaryote HGT is especially easy to spot (Figure 1). At the same time, however, bacteria are also abundant in nearly all environments, and many eukaryotes survive by eating and digesting them in large numbers, so it is also reasonable to assume that bacterial genomes are the most common potential source of foreign genetic material for eukaryotes. Eukaryote-to-eukaryote transfer, as well as serial transfers (Figure 1) are not unknown, but remain relatively rare [15,18••,19,20•,21•,22–28].

Gene replacement versus introduction of a new function

Many cases of HGT in eukaryotes involve the acquisition of a gene that was already present in the genome, in

Box 1 HGT and the human genome

Clear evidence for HGT in animals, with a few glaring exceptions [58], continues to be relatively rare. However, when the draft human genome was first reported, one of the more shocking claims was that hundreds of genes were derived via HGT [59]. This claim was made on the basis of distribution: human genes that had homologues in bacteria but not in other completely sequenced non-vertebrate genomes were interpreted as being derived from HGT from bacteria relatively recently, during the evolution of vertebrates. However, this claim was almost immediately disputed. In many cases incompletely sequenced eukaryotic genomes were found to contain genes more closely related to the vertebrate homologues than were the bacterial counterparts [60,61]. This case may be the most infamous, but it is only one of several where relatively crude approaches to detecting HGT have resulted in misleading claims, and which have collectively tainted many stronger cases in people's minds.

particular those cases involving 'core' processes like translation or central metabolism [8,9,15,17,29]. In such cases, a new gene simply replaces an existing homologue, and it is not always clear whether there has been any benefit derived from the transfer. In contrast, the acquisition of a completely new gene or pathway (Figure 1) can lead to an obvious and immediate benefit, which can sometimes be compellingly linked to the ecology and life history of the recipient organism. This review will examine some recent data on transfers where some argument for an adaptive benefit can be made, and these cases fall into two overlapping themes: the adaptation of organisms to the stresses of a particular environment and, a subset of these, the evolution of parasitism and pathogenesis.

Box 2 Potential problems in identifying HGT

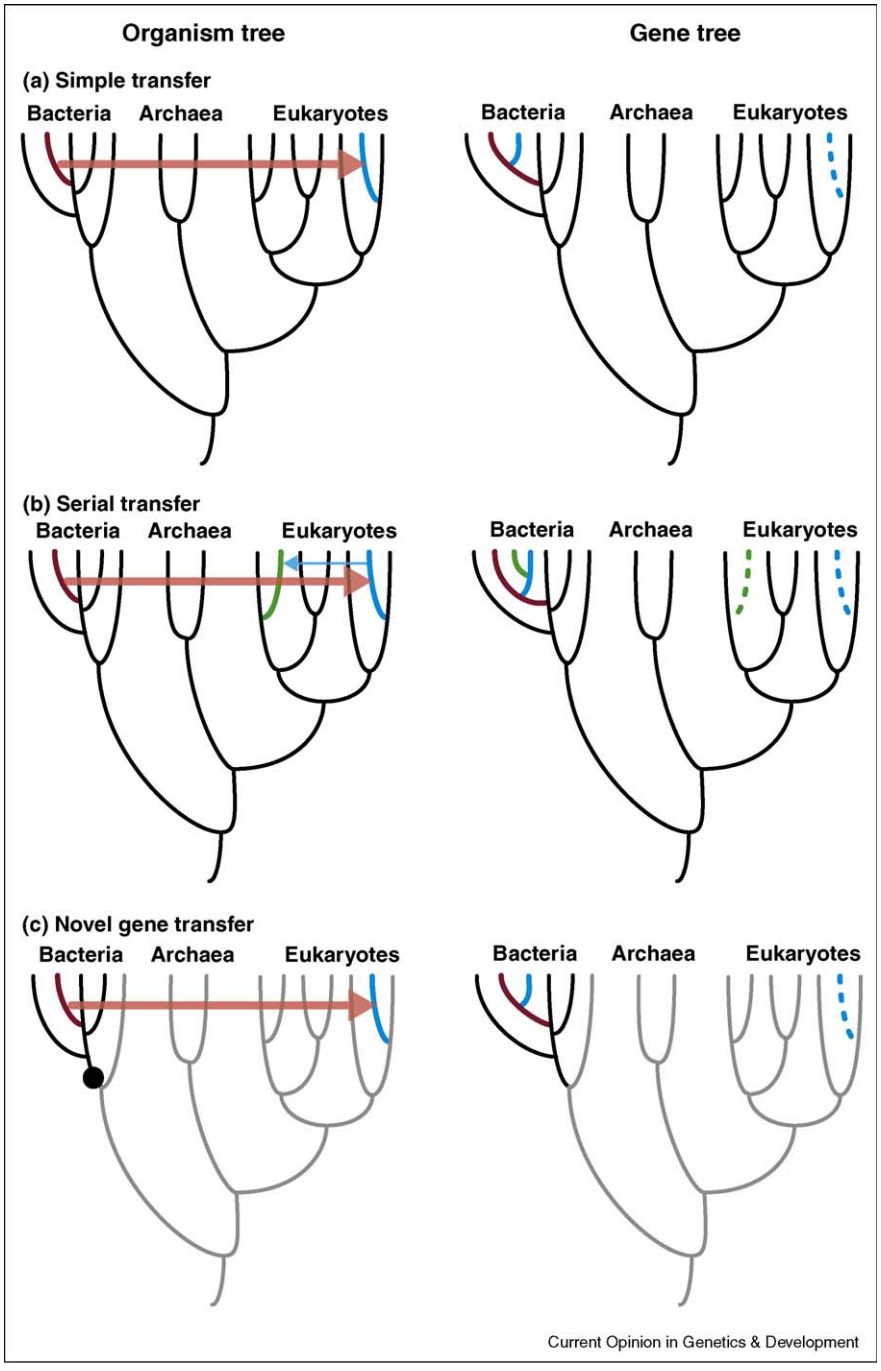
There are several ways to detect HGT, but the best is a phylogenetic tree that strongly contradicts our expectations for the organisms. There are many so-called surrogate methods, but these have been shown to be error-prone [62], and sometimes led to disastrously misleading conclusions (see Box 1). Even with a well-supported phylogeny, however, there are several ways in which one might be mislead by incomplete sampling. On one hand, misleading data might lead to erroneous conclusions, such as contaminating sequences masquerading as HGT [63,64], which may even appear in complete genomes [65]. On the other hand, even with accurate data the distribution of a gene in nature can confound our interpretation. For example, gene duplication and differential loss of the resulting paralogues can lead to a phylogeny where two distantly related lineages branch together. Even more commonly, however, the problem rests with how shallow is our current sampling of biological diversity. Additional sampling can either reveal formerly hidden diversity or paralogy, or change the topology of the inferred tree, in either case potentially transforming what appears to be an HGT event into vertical descent [66,67]. Because our interpretation of HGT is always tied to sampling, alternatives to HGT can seldom ever be excluded outright. For individual cases the likelihood of each alternative must be weighed, but there are some obvious criteria with which to judge. For example, more recent events and more distantly related donor and recipient lineages both allow one to make a stronger case for HGT.

HGT in the adaptation to environmental conditions

The role of HGT in allowing bacteria to adapt to particular environments is well known. This is exemplified by the high level of HGT observed in the genome of the thermoacidophile *Thermotoga*, which has acquired genes relating to its environment and metabolism from archaebacteria inhabiting similar environments [30,31]. The possible role of HGT in adapting to such an unusual environment is not hard to imagine, and indeed, the narrower the niche the easier it is to see the effects of transfer. Perhaps the most comparable case in eukaryotes is the adaptation to anaerobiosis. A number of eukaryotic lineages have fully or partially shed oxidative respiration and instead rely on variations of substrate-level phosphorylation and fermentation. These transitions have taken place several times in evolution, and the enzymes underpinning this metabolism are now known to have been acquired from various sources, many by HGT [10,32,33]. In one rumen environment, a very high level of HGT has been recorded [34]. The multiple independent assembly of these systems by 'tinkering' makes for an interesting examination of HGT in converging systems. For example, many anaerobes have replaced two ATP-dependent enzymes in glycolysis with pyrophosphate-dependent analogues, presumably to increase the efficiency of a pathway under energy-limited conditions. In both cases, the eukaryotic enzymes can be traced back to multiple different bacterial groups, indicating several convergent origins through HGT [35–37]. Other oddities of anaerobic metabolism are also derived from HGT, and many of them appear to have originated though several independent transfers [38]. One of the more interesting enzymes is hydrogenase, which reduces protons to form hydrogen gas. Eukaryotes have seemingly acquired hydrogenase from more than one HGT event, but in the anaerobic ciliate *Nyctotherus*, the enzyme is itself composed of several modules that were each acquired through HGT from different sources and assembled into one mosaic enzyme [39•].

Anaerobiosis presents so many obvious cases because even those functions we take to be fundamental in other systems have been replaced with new ones, but HGT has also played an important role in adaptation in mesophilic environments. Little is known about the genomes of most soil-dwelling eukaryotes, but there are indications that HGT is important in soil microbial ecology. A handful of bacterial genes relating to digestion and self-defence were identified in the genome of the slime mould *Dictyostelium* [13], and exchanges between fungi and other saprophytes are also known (see below). In some cases, an entire pathway rather than a single gene has been acquired, which may facilitate a shift in the nutritional mode of the recipient. For example, the ascomycete fungus *Trichoderma* appears to have acquired a fully assembled nitrate assimilation gene cluster from a distantly related basidiomycete [21•].

Figure 1



Examples of different HGT events (right), and how they appear in molecular phylogenetic reconstruction (left). Case **(a)** shows a relatively simple case of a gene moving to a distantly related lineage (in this case a bacterial gene moving to a eukaryote) and replacing an existing homologue. In the phylogenetic tree based on that gene, the one eukaryotic lineage (blue) falls far from its expected location with other eukaryotes and is instead closely related to a particular lineage of bacteria (red), from which the gene was acquired. This is the easiest type of HGT to detect, and the type for which the strongest evidence exists. Case **(b)** shows a more complex serial transfer. Here a bacterial gene (red) has moved to a eukaryote (blue), replacing its homologue, and then second eukaryote (green) has acquired this gene from the first eukaryotic recipient. The result is two distantly related eukaryotes sharing a gene that is closely related to bacterial homologues. This type of transfer is much harder to interpret, and in some instances inadequate sampling has led to such transfers being initially interpreted as simple events (like Case **(a)**). Both the above cases involve genes that are universally distributed, but this is not always true, and generally less important in the acquisition of new functions. In case **(c)**, the gene in question originated within a subset of bacteria by some means (at the black dot) and is not found in other lineages (grey lines). If a copy of this gene (red) is then acquired by another lineage (blue), the result is a 'patchy' distribution [57] where the gene is found in only a few organisms, and they are not closely related. This type of transfer is very important in the acquisition of new functions, and patchy distribution can be combined with serial transfer to create even more complex routes of information flow throughout the tree [20•].

Inhabitants of the marine environment are better studied at the genomic level, and here HGT has emerged as a clear factor in the adaptation to various stresses. Nutritionally, two of the major limitations for marine microbes are iron and nitrogen [40]. Iron-stress especially has been the focus of recent attention, as it is known to be the limiting nutrient in large areas of surface waters, where seeding leads to massive algal blooms, particularly diatoms [41]. The blooms that result from this seeding are dominated by a subset of pennate diatoms, and it has now been shown that the genomes of several of these species encode a gene for the iron-concentrating protein ferritin, which is absent in close relatives [42••]. Ferritin appears to not only help protect these species from spikes in iron concentration by sequestering it, but also allow the organisms to store iron safely for use when it is a limiting nutrient. The conclusion that diatom ferritin is derived from HGT is based mostly on its limited and patchy distribution (Figure 1c), and although further sampling might reveal a broader distribution, the diatom genes is still not closely related to homologues in other eukaryotes [42••]. A similar situation is found in a putative ferrichrome-binding protein in diatoms, which is highly similar to a bacterial iron-import protein and appears to mediate the uptake of siderophore-bound iron, and further supports an important role for HGT in adaptation to iron-limited environments [43•].

Nitrogen is a limiting nutrient in other regions of the oceans, and evidence is now also emerging for HGT allowing eukaryotic algae to cope with this stress. One clear case of HGT comes once again from diatoms, where a bacterial carbamate kinase has been recruited as an entry point to the urea cycle [44], and the complete genome of the diatom *Phaeodactylum* revealed HGT played a role in shaping many aspects of nitrogen metabolism [45•]. Interestingly, in marine green algae, which are distantly related to diatoms, evidence for HGT shaping nitrogen metabolism has also emerged. In comparisons between two strains of the ubiquitous marine green picoplankton *Micromonas* HGT was found to have played a role in many aspects of their evolution [46•], but one class of genes of particular interest are ammonium transporters (A Worden, unpublished data).

The cases above all stress the frequency of HGT in microbial eukaryotes, but this is not to say it is completely absent from large, multicellular eukaryotes. Indeed, one intriguing case where HGT provides a clear function advantage is in the acquisition of antifreeze proteins (AFPs) in arctic fish. A variety of AFPs have evolved convergently in response to life in cold waters, but a subset of AFPs appear to have evolved once from a lectin-like protein, and then spread by HGT between distantly related fish species [18••]. In this case, not only is the distribution of the APF amongst fish extremely patchy, but the phylogeny of the AFP is also not consistent with that of the fish, so a process of fish-to-fish HGT best explains the data. Whilst it is clear why the transfer of a AFP might be favourable to cold-water fish, it is unclear how a gene could move from one vertebrate lineage into another and become integrated into the germ line, although a case has been made for such transfers occasionally [47].

HGT in adaptation to a parasitic/pathogenic way of life

The adaptation of parasites and pathogens to their host organism in many ways represents a subclass of organisms adapting to the stresses of their environment discussed above, but one where the stresses are well defined, studied in detail, and as a result offer interesting insights in the role of HGT in such adaptation. Indeed, the first cases of HGT in bacteria were drug-resistance genes [1], and the movement of other kinds of genes related to virulence led to the concept of mobile 'pathogenecity islands' [48]. In both case, the practical advantage to mobility, both to the pathogen and the genes themselves, are obvious and their rapid dissemination can be explained by selection. In eukaryotes as well, some of the first cases of HGT were associated with parasitism [5,6], and virulence factors and genes conferring drug resistance have been documented to move between pathogens. In one of the more dramatic cases, an avirulent fungus acquired an 11 kb fragment from a pathogenic relative only 70 years ago, creating a new pathogenic variety through a single, recent transfer event [25].

In addition to conferring virulence, HGT has also enabled parasites to invade new host 'environments' in many other ways. There is a wide variety of cases where parasites acquired genes allowing them to capitalize on new energy sources or survive environmental stresses [49–53]. Some of these may trace back to the origin of the parasitic group, and might help explain how they made the transition from free-living to parasitic. The metabolic shift in the various anaerobes discussed above is one example, since the majority of these organisms are parasites adapted to the anaerobic conditions prevailing within animals, so it is likely that the transition to anaerobiosis was co-incident with their transition to parasitism. A similar case can be made for oomycetes, where a number of genes involved in the osmotrophic absorption of nutrients have been shown to have been acquired from saprophytic fungi by HGT, events linked to the origin of plant parasitism in this group [23].

Whilst on one hand HGT to parasites represents their ability to adapt to new stresses and better exploit their host, transferred genes also might be a weakness that we may exploit in fighting infections. This duality is exemplified in the ability to scavenge nucleotides. The human parasite *Cryptosporidium* has acquired nucleotide salvage pathway genes from bacteria that allows it to survive

without *de novo* synthesis [54,55]. At the same time, however, this acquisition provides us with biochemical activities that are absent or distantly related to any activities of the animal host, making it an ideal target for drugs. This concept was applied to the *Cryptosporidium* inosine-5′-monophosphate dehydrogenase (IMPDH), the rate-limiting step in guanine synthesis, leading to the identification of four new drugs that are more potent than current anti-cryptosporidial agents [56••].

Concluding remarks: HGT as a means to adaptation

Acquiring a new gene or set of functionally related genes can benefit an organism in several ways, but there are common themes relating to how this might take place. Whether an organism is invading a new environment or simply getting a leg-up on its competitors in an environment where its ancestors have long thrived, the most straightforward source of useful genetic information is from other organisms already adapted to that environment. This is in part due to simple opportunity, because the probability of acquiring genes from a neighbour is higher, especially if you are eating them, but is also due to the fact that genes that confer some benefit to living in the specific set of circumstances that make up that environment are more likely to be found in other organisms already adapted to those circumstances. Thus the ecological link between donor and recipient lineages may be twofold.

In all likelihood, this ecological link partly explains the observation that HGT to eukaryotes predominantly involves genes derived from bacteria. Whilst it is still true that sampling and detection issues probably play a role in this, it is not unreasonable that bacterial genes still dominate HGT to nuclear genomes. Indeed, this dominance of bacterial genes is amplified in the case of transfers that involve the addition of novel functions. This probably stems from the fact that bacteria are metabolically more diverse than eukaryotes, and as such have much more to offer in the way of new and useful functions. To acquire new metabolic capabilities from another eukaryote is less likely since there are fewer such novelties to be had, although exceptions do exist [23,25]. It is also still possible for serial transfers to move novel functions between eukaryotes even though they are ultimately derived from bacteria (Figure 1), and this seems to have happened in some cases [20•]. However, the current evidence for convergent adaptations where multiple eukaryotic lineages independently acquire the same new gene from different bacteria by HGT is stronger, altogether suggesting the major route of transfer of new functions to eukaryotes is directly from bacteria.

Acknowledgements

I wish to thank Alexandra Worden and Andrew Allen for discussions and sharing their unpublished observations. Work on HGT in the Keeling laboratory is supported by the Canadian Institutes for Health Research, the Natural Sciences and Engineering Research Council of Canada and the Tula Foundation through the Centre for Microbial Diversity and Evolution. PJK is a Senior Scholar of the Michael Smith Foundation for Health Research and a Fellow of the Canadian Institute for Advanced Research.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Akiba T, Koyama K, Ishiki Y, Kimura S, Fukushima T: **On the mechanism of the development of multiple-drug-resistant clones of *Shigella***. *Jpn J Microbiol* 1960, **4**:219-227.

2. Doolittle WF: **Phylogenetic classification and the universal tree**. *Science* 1999, **284**:2124-2129.

3. Lawrence JG, Hendrickson H: **Lateral gene transfer: when will adolescence end?** *Mol Microbiol* 2003, **50**:739-749.

4. Lawrence JG: **Gene transfer in bacteria: speciation without species?** *Theor Popul Biol* 2002, **61**:449-460.

5. Andersson JO: **Lateral gene transfer in eukaryotes**. *Cell Mol Life Sci* 2005, **62**:1182-1197.

6. Richards TA, Hirt RP, Williams BA, Embley TM: **Horizontal gene transfer and the evolution of parasitic protozoa**. *Protist* 2003, **154**:17-32.

7. •• Keeling PJ, Palmer JD: **Horizontal gene transfer in eukaryotic evolution**. *Nat Rev Genet* 2008, **9**:605-618.
A recent review of HGT to eukaryotes in general, including the effects of endosymbiosis.

8. Archibald JM, Rogers MB, Toop M, Ishida K, Keeling PJ: **Lateral gene transfer and the evolution of plastid-targeted proteins in the secondary plastid-containing alga *Bigelowiella natans***. *Proc Natl Acad Sci U S A* 2003, **100**:7678-7683.

9. Bergthorsson U, Richardson AO, Young GJ, Goertzen LR, Palmer JD: **Massive horizontal transfer of mitochondrial genes from diverse land plant donors to the basal angiosperm *Amborella***. *Proc Natl Acad Sci U S A* 2004, **101**:17747-17752.

10. Loftus B, Anderson I, Davies R, Alsmark UC, Samuelson J, Amedeo P, Roncaglia P, Berriman M, Hirt RP, Mann BJ *et al.*: **The genome of the protist parasite *Entamoeba histolytica***. *Nature* 2005, **433**:865-868.

11. Richardson AO, Palmer JD: **Horizontal gene transfer in plants**. *J Exp Bot* 2007, **58**:1-9.

12. Berriman M, Ghedin E, Hertz-Fowler C, Blandin G, Renauld H, Bartholomeu DC, Lennard NJ, Caler E, Hamlin NE, Haas B *et al.*: **The genome of the African trypanosome *Trypanosoma brucei***. *Science* 2005, **309**:416-422.

13. Eichinger L, Pachebat JA, Glockner G, Rajandream MA, Sucgang R, Berriman M, Song J, Olsen R, Szafranski K, Xu Q *et al.*: **The genome of the social amoeba *Dictyostelium discoideum***. *Nature* 2005, **435**:43-57.

14. Jain R, Rivera MC, Lake JA: **Horizontal gene transfer among genomes: the complexity hypothesis**. *Proc Natl Acad Sci U S A* 1999, **96**:3801-3806.

15. Keeling PJ, Inagaki Y: **A class of eukaryotic GTPase with a punctate distribution suggesting multiple functional replacements of translation elongation factor 1alpha**. *Proc Natl Acad Sci U S A* 2004, **101**:15380-15385.

16. Gile GH, Faktorova D, Castlejohn CA, Burger G, Lang BF, Farmer MA, Lukes J, Keeling PJ: **Distribution and phylogeny of EFL and EF-1alpha in Euglenozoa suggest ancestral co-occurrence followed by differential loss**. *PLoS ONE* 2009, **4**:e5162.

17. Xie J, Fu Y, Jiang D, Li G, Huang J, Li B, Hsiang T, Peng Y: **Intergeneric transfer of ribosomal genes between two fungi**. *BMC Evol Biol* 2008, **8**:87.

18. Graham LA, Lougheed SC, Ewart KV, Davies PL: **Lateral transfer**
•• **of a lectin-like antifreeze protein gene in fishes**. *PLoS ONE* 2008, **3**:e2616.
A rare case of HGT in vertebrates, in this case between different fish. The authors describe a patchy distribution of antifreeze proteins that, together with the phylogeny of the enzyme, suggests the gene has been moved between distantly related cold-water fish species.

19. Sanchez-Perez GF, Hampl V, Simpson AG, Roger AJ: **A new divergent type of eukaryotic methionine adenosyltransferase is present in multiple distantly related secondary algal lineages**. *J Eukaryot Microbiol* 2008, **55**:374-381.

20. Rogers MB, Watkins RF, Harper JT, Durnford DG, Gray MW,
• Keeling PJ: **A complex and punctate distribution of three eukaryotic genes derived by lateral gene transfer**. *BMC Evol Biol* 2007, **7**:89.
An illustration of how complex cases that appear to be serial transfer events can at first look like simple HGT from bacteria to eukaryotes.

21. Slot JC, Hibbett DS: **Horizontal transfer of a nitrate assimilation**
• **gene cluster and ecological transitions in fungi: a phylogenetic study**. *PLoS ONE* 2007, **2**:e1097.
Acquiring whole biochemical pathways would be more beneficial than many individual genes, and in this paper such a transfer is described in fungi.

22. Andersson JO, Sjogren AM, Horner DS, Murphy CA, Dyal PL, Svard SG, Logsdon JM Jr, Ragan MA, Hirt RP, Roger AJ: **A genomic survey of the fish parasite *Spironucleus salmonicida* indicates genomic plasticity among diplomonads and significant lateral gene transfer in eukaryote genome evolution**. *BMC Genomics* 2007, **8**:51.

23. Richards TA, Dacks JB, Jenkinson JM, Thornton CR, Talbot NJ: **Evolution of filamentous plant pathogens: gene exchange across eukaryotic kingdoms**. *Curr Biol* 2006, **16**:1857-1864.

24. Richards TA, Dacks JB, Campbell SA, Blanchard JL, Foster PG, McLeod R, Roberts CW: **Evolutionary origins of the eukaryotic shikimate pathway: gene fusions, horizontal gene transfer, and endosymbiotic replacements**. *Eukaryot Cell* 2006, **5**:1517-1531.

25. Friesen TL, Stukenbrock EH, Liu Z, Meinhardt S, Ling H, Faris JD, Rasmussen JB, Solomon PS, McDonald BA, Oliver RP: **Emergence of a new disease as a result of interspecific virulence gene transfer**. *Nat Genet* 2006, **38**:953-956.

26. Inderbitzin P, Harkness J, Turgeon BG, Berbee ML: **Lateral transfer of mating system in *Stemphylium***. *Proc Natl Acad Sci U S A* 2005, **102**:11390-11395.

27. Nedelcu AM, Miles IH, Fagir AM, Karol K: **Adaptive eukaryote-to-eukaryote lateral gene transfer: stress-related genes of algal origin in the closest unicellular relatives of animals**. *J Evol Biol* 2008, **21**:1852-1860.

28. Simpson AG, Perley TA, Lara E: **Lateral transfer of the gene for a widely used marker, alpha-tubulin, indicated by a multi-protein study of the phylogenetic position of *Andalucia* (Excavata)**. *Mol Phylogenet Evol* 2008, **47**:366-377.

29. Hackett JD, Yoon HS, Soares MB, Bonaldo MF, Casavant TL, Scheetz TE, Nosenko T, Bhattacharya D: **Migration of the plastid genome to the nucleus in a peridinin dinoflagellate**. *Curr Biol* 2004, **14**:213-218.

30. Nelson KE, Clayton RA, Gill SR, Gwinn ML, Dodson RJ, Haft DH, Hickey EK, Peterson JD, Nelson WC, Ketchum KA *et al.*: **Evidence for lateral gene transfer between Archaea and bacteria from genome sequence of *Thermotoga maritima***. *Nature* 1999, **399**:323-329.

31. Zhaxybayeva O, Swithers KS, Lapierre P, Fournier GP, Bickhart DM, DeBoy RT, Nelson KE, Nesbo CL, Doolittle WF, Gogarten JP *et al.*: **On the chimeric nature, thermophilic origin, and phylogenetic placement of the Thermotogales**. *Proc Natl Acad Sci U S A* 2009, **106**:5865-5870.

32. Carlton JM, Hirt RP, Silva JC, Delcher AL, Schatz M, Zhao Q, Wortman JR, Bidwell SL, Alsmark UC, Besteiro S *et al.*: **Draft genome sequence of the sexually transmitted pathogen *Trichomonas vaginalis***. *Science* 2007, **315**:207-212.

33. Morrison HG, McArthur AG, Gillin FD, Aley SB, Adam RD, Olsen GJ, Best AA, Cande WZ, Chen F, Cipriano MJ *et al.*: **Genomic minimalism in the early diverging intestinal parasite *Giardia lamblia***. *Science* 2007, **317**:1921-1926.

34. Ricard G, McEwan NR, Dutilh BE, Jouany JP, Macheboeuf D, Mitsumori M, McIntosh FM, Michalowski T, Nagamine T, Nelson N *et al.*: **Horizontal gene transfer from Bacteria to rumen Ciliates indicates adaptation to their anaerobic, carbohydrates-rich environment**. *BMC Genomics* 2006, **7**:22.

35. Slamovits CH, Keeling PJ: **Pyruvate-phosphate dikinase of oxymonads and parabasalia and the evolution of pyrophosphate-dependent glycolysis in anaerobic eukaryotes**. *Eukaryot Cell* 2006, **5**:148-154.

36. Stechmann A, Baumgartner M, Silberman JD, Roger AJ: **The glycolytic pathway of *Trimastix pyriformis* is an evolutionary mosaic**. *BMC Evol Biol* 2006, **6**:101.

37. Muller M, Lee JA, Gordon P, Gaasterland T, Sensen CW: **Presence of prokaryotic and eukaryotic species in all subgroups of the PP(i)-dependent group II phosphofructokinase protein family**. *J Bacteriol* 2001, **183**:6714-6716.

38. Barbera MJ, Ruiz-Trillo I, Leigh J, Hug LA, Roger AJ: **The diversity of mitochondrion-related organelles amongst eukaryotic microbes**. In *Origins of Mitochondria and Hydrogenosomes.* Edited by Martin W, Müller M. Springer-Verlag; 2007:239-268.

39. Boxma B, Ricard G, van Hoek AH, Severing E, Moon-van der
• Staay SY, van der Staay GW, van Alen TA, de Graaf RM, Cremers G, Kwantes M *et al.*: **The [FeFe] hydrogenase of *Nyctotherus ovalis* has a chimeric origin**. *BMC Evol Biol* 2007, **7**:230.
The distribution of hydrogenase genes in eukaryotes has suggested they may be prone to HGT, but in this paper the authors suggest that various domains of a single hydrogenase enzyme were derived from several HGT events from different sources.

40. Parker MS, Mock T, Armbrust EV: **Genomic insights into marine microalgae**. *Annu Rev Genet* 2008, **42**:619-645.

41. Coale KH, Johnson KS, Fitzwater SE, Gordon RM, Tanner S, Chavez FP, Ferioli L, Sakamoto C, Rogers P, Millero F *et al.*: **A massive phytoplankton bloom induced by an ecosystem-scale iron fertilization experiment in the equatorial Pacific Ocean**. *Nature* 1996, **383**:495-501.

42. Marchetti A, Parker MS, Moccia LP, Lin EO, Arrieta AL, Ribalet F,
•• Murphy ME, Maldonado MT, Armbrust EV: **Ferritin is used for iron storage in bloom-forming marine pennate diatoms**. *Nature* 2009, **457**:467-470.
Iron is the limiting nutrient in much of the ocean, and in this paper the authors show that marine diatoms that bloom in response to iron encode a gene for ferritin. Ferritin allows these organisms to sequester iron during times of abundance and store it for times of need, explaining why they bloom.

43. Allen AE, Laroche J, Maheswari U, Lommer M, Schauer N,
• Lopez PJ, Finazzi G, Fernie AR, Bowler C: **Whole-cell response of the pennate diatom *Phaeodactylum tricornutum* to iron starvation**. *Proc Natl Acad Sci U S A* 2008, **105**:10438-11043.
As with Ref. [42••], this paper shows diatoms acquired a gene allowing them to utilize rare iron resources by HGT.

44. Allen JF, Puthiyaveetil S, Strom J, Allen CA: **Energy transduction anchors genes in organelles**. *Bioessays* 2005, **27**:426-435.

45. Bowler C, Allen AE, Badger JH, Grimwood J, Jabbari K, Kuo A,
• Maheswari U, Martens C, Maumus F, Otillar RP *et al.*: **The *Phaeodactylum* genome reveals the evolutionary history of diatom genomes**. *Nature* 2008, **456**:239-244.
The complete genome of a diatom, which contains a number of genes derived by HGT, many of which affect the organisms ability to cope with nitrogen metabolism.

46. Worden AZ, Lee JH, Mock T, Rouze P, Simmons MP, Aerts AL,
• Allen AE, Cuvelier ML, Derelle E, Everett MV *et al.*: **Green evolution and dynamic adaptations revealed by genomes of the marine picoeukaryotes *Micromonas***. *Science* 2009, **324**:268-272.
As with Ref. [45•], the genomes of two marine green algae acquired many genes via HGT, and a number of these are involved in nitrogen metabolism.

47. Alvarez N, Benrey B, Hossaert-McKey M, Grill A, McKey D, Galtier N: **Phylogeographic support for horizontal gene**

transfer involving sympatric bruchid species. *Biol Direct* 2006, **1**:21.

48. Hacker J, Blum-Oehler G, Muhldorfer I, Tschape H: **Pathogenicity islands of virulent bacteria: structure, function and impact on microbial evolution**. *Mol Microbiol* 1997, **23**:1089-1097.

49. de Koning AP, Brinkman FS, Jones SJ, Keeling PJ: **Lateral gene transfer and metabolic adaptation in the human parasite *Trichomonas vaginalis***. *Mol Biol Evol* 2000, **17**:1769-1773.

50. Huang J, Mullapudi N, Sicheritz-Ponten T, Kissinger JC: **A first glimpse into the pattern and scale of gene transfer in Apicomplexa**. *Int J Parasitol* 2004, **34**:265-274.

51. Rogers MB, Keeling PJ: **Lateral gene transfer and re-compartmentalisation of Calvin cycle enzymes in plants and algae**. *J Mol Evol* 2003, **58**:367-375.

52. Fast NM, Law JS, Williams BA, Keeling PJ: **Bacterial catalase in the microsporidian *Nosema locustae*: implications for microsporidian metabolism and genome evolution**. *Eukaryot Cell* 2003, **2**:1069-1075.

53. Slamovits CH, Keeling PJ: **Class II photolyase in a microsporidian intracellular parasite**. *J Mol Biol* 2004, **341**:713-721.

54. Striepen B, White MW, Li C, Guerini MN, Malik SB, Logsdon JM Jr, Liu C, Abrahamsen MS: **Genetic complementation in apicomplexan parasites**. *Proc Natl Acad Sci U S A* 2002, **99**:6304-6309.

55. Striepen B, Pruijssers AJ, Huang J, Li C, Gubbels MJ, Umejiego NN, Hedstrom L, Kissinger JC: **Gene transfer in the evolution of parasite nucleotide biosynthesis**. *Proc Natl Acad Sci U S A* 2004, **101**:3154-3159.

56. •• Umejiego NN, Gollapalli D, Sharling L, Volftsun A, Lu J, Benjamin NN, Stroupe AH, Riera TV, Striepen B, Hedstrom L: **Targeting a prokaryotic protein in a eukaryotic pathogen: identification of lead compounds against cryptosporidiosis**. *Chem Biol* 2008, **15**:70-77.

Parasites have acquired many genes from bacteria, and in this paper the authors characterize the function of one such gene in a human parasite. They show the gene, distantly related to anything in the human host, is sensitive to a number of drugs, providing new possibilities to treat the infection.

57. Andersson JO, Hirt RP, Foster PG, Roger AJ: **Evolution of four gene families with patchy phylogenetic distributions: influx of genes into protist genomes**. *BMC Evol Biol* 2006, **6**:27.

58. Gladyshev EA, Meselson M, Arkhipova IR: **Massive horizontal gene transfer in bdelloid rotifers**. *Science* 2008, **320**:1210-1213.

59. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, Devon K, Dewar K, Doyle M, FitzHugh W *et al.*: **Initial sequencing and analysis of the human genome**. *Nature* 2001, **409**:860-921.

60. Salzberg SL, White O, Peterson J, Eisen JA: **Microbial genes in the human genome: lateral transfer or gene loss?** *Science* 2001, **292**:1903-1906.

61. Roelofs J, Van Haastert PJ: **Genes lost during evolution**. *Nature* 2001, **411**:1013-1014.

62. Ragan MA, Harlow TJ, Beiko RG: **Do different surrogate methods detect lateral genetic transfer events of different relative ages?** *Trends Microbiol* 2006, **14**:4-8.

63. Willerslev E, Mourier T, Hansen AJ, Christensen B, Barnes I, Salzberg SL: **Contamination in the draft of the human genome masquerades as lateral gene transfer**. *DNA Seq* 2002, **13**:75-76.

64. Skaar EP, Seifert HS: **The misidentification of bacterial genes as human cDNAs: was the human D-1 tumor antigen gene acquired from bacteria?** *Genomics* 2002, **79**:625-627.

65. Rice DW, Palmer JD: **An exceptional horizontal gene transfer in plastids: gene replacement by a distant bacterial paralog and evidence that haptophyte and cryptophyte plastids are sisters**. *BMC Biol* 2006, **4**:31.

66. Gamieldien J, Ptitsyn A, Hide W: **Eukaryotic genes in *Mycobacterium tuberculosis* could have a role in pathogenesis and immunomodulation**. *Trends Genet* 2002, **18**:5-8.

67. Kinsella RJ, McInerney JO: **Eukaryotic genes in *Mycobacterium tuberculosis*? Possible alternative explanations**. *Trends Genet* 2003, **19**:687-689.