

and we see the 'edge' of the jet. At this point, a plot of brightness against time (light curve) shows a sudden change in slope, growing fainter more quickly because no new emitting material is coming into view (Fig. 1). Such a 'break' in the light curve occurs simultaneously at all wavelengths.

The timing of this break in the afterglow light curve is now known for about 17 GRBs, for which Frail and colleagues² calculate jet opening angles of 2–25°, mostly around 4°. There is a strong relationship between the opening angle and the brightness of the GRB. For example, the brightest GRB known to date, GRB990123, also has one of the smallest opening angles, 2.9°. Frail *et al.* show that the fraction of the sky covered by the jet multiplied by the total energy the burst would have had if it had come from a sphere gives a roughly constant energy value of 5×10^{43} J. This value appears to be typical of most GRBs, and is several thousand times smaller than the energy previously required for GRB990123.

But if a typical burst is visible to only a small fraction of observers, we have to assume that there are far more GRBs than we observe. Frail *et al.* reckon that, for every burst we see, about 500 point in another direction. This means that there are at least 1,500 GRBs every day in the visible Universe, roughly corresponding to the birth of a stellar-mass black hole every minute. This is possible if about 1% of those stars massive enough to die as supernovae end up as GRBs, a reasonable assumption.

This is not quite the whole story — there is still some uncertainty about the efficiency with which the energy of the fast-moving jets is converted into gamma rays¹⁰. Frail *et al.* assume a typical value of 20%, which gives a jet energy of 2.5×10^{44} J. But the efficiency might be expected to vary from event to event, and to depend on the opening angle. They also assume that the density of matter surrounding the GRB is constant, whereas it probably declines with distance. It would also be surprising if the jet were uniform in brightness. Frail *et al.* assume that the opening angle does not vary with time and that Γ does not change with time or opening angle, although models predict that Γ declines from the middle of the jet to its edge and that the angle itself increases with time.

Nonetheless, similar conclusions regarding a standard energy for GRBs have also been reached by others^{11,12}, so it is likely that GRBs, although not standard candles, are almost standard 'bombs'. The jet energy calculated by Frail *et al.* (2.5×10^{44} J) is about twice that of a supernova, but this is just the material moving fast enough to contribute to the afterglow. GRB990123 probably has several times this amount, and even more energy might be released as slower material, especially if the jet has to bore through the remains of its parent star⁷. So the true total

energy of a bright GRB is still probably ten times greater than that of an ordinary supernova, allowing them to keep the title of nature's grandest explosions. ■

Stan Woosley is in the Department of Astronomy and Astrophysics, University of California at Santa Cruz, Santa Cruz, California 95064, USA.

e-mail: woosley@ucolick.org

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The human genome

Part three in the book of genes

Masahira Hattori and Todd D. Taylor

Working out the draft sequence of the human genome was a landmark achievement. But there's lots more to be done before the finished product is available. The complete sequence of chromosome 20 sets us on the way.

Believe it or not, the Harry Potter stories aren't the only highly anticipated series being published these days. On page 865 of this issue¹, you can find the third instalment in another such series — the book of human genes. This book is being produced by thousands of people around the globe, and began two years ago with the publication of the complete DNA sequence of chromosome 22 by part of the publicly funded International Human Genome Sequencing Consortium². The second instalment³, detailing the sequence of chromosome 21, came in May 2000, and in February this year we had two previews of the whole human genome in draft form — one produced by the publicly funded project⁴ and the other by Celera Genomics⁵.

Chromosome 20 is the third chromosome to be completely sequenced as part of the public project, and is the longest of the three

that have been finished so far — nearly 60 million bases (megabases), some 2% of the human genome. As Deloukas and colleagues¹ describe, they have sequenced roughly 99.5% of the gene-active ('euchromatic') regions of chromosome 20, leaving only four physical gaps spanning about 320 kilobases. (This excludes the centromere — the main constriction along the chromosome, which is important in cell division but is repetitive and nearly impossible to sequence.) The four gaps may contain sequences that are rich in guanine (G) and cytosine (C) bases and are also difficult to tackle with current technologies. The number and total size of gaps are intermediate between those that remain unsequenced on chromosomes 21 and 22, but given the larger size of chromosome 20 it is quite an achievement. The authors also identified ('annotated') 727 genes on chromosome 20, which gives a density of 12 genes

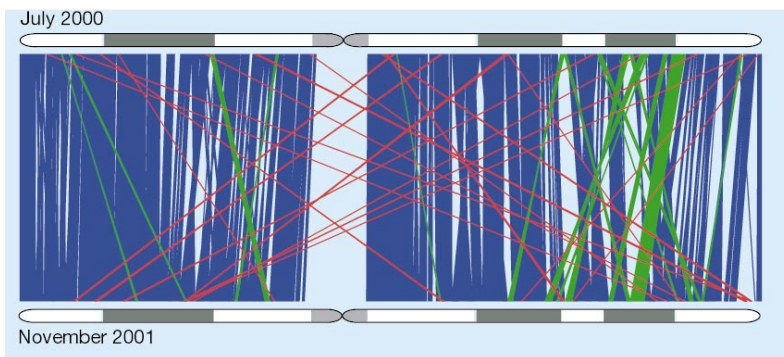


Figure 1 Chromosome 20, from draft to finished quality. The draft data obtained by the publicly funded human genome project⁴ were aligned with the current finished sequence¹. Each line between the two diagrams of the chromosome indicates the same piece of sequence. Colours represent how much the sequence position has shifted between versions (blue, less than 3 megabases; green, 3–10 megabases; red, more than 10 megabases). The ideograms represent the typical banding pattern for chromosome 20, as stained with the dye Giemsa. The light grey region represents the centromere; the white bands are generally rich in G+C bases and dense with genes; the dark grey bands are generally rich in A+T bases and gene-poor. (The figure was prepared by Takehiko Ito, Mitsubishi Research Institute.)

per megabase (compared with the 16.3 genes per megabase on chromosome 22, and 6.7 on chromosome 21).

Deloukas *et al.* analysed the sequence of chromosome 20 with methods similar to those used for the other chromosomes²⁻⁵. But they also introduced new approaches; for example, they compared the sequence with newly released genome data from species such as mice⁶ and puffer fish⁷. Comparing sequences between evolutionarily disparate species reveals genomic sites that have not been able to change much during evolution, because they have essential functions. Such sites are often genes or gene-regulatory elements, and most (even though they are often shorter than 50 bases) are found at similar positions in different genomes. So comparative analyses can be superior to more traditional methods such as computer predictions in allowing unknown genes and regulatory elements to be annotated. And comparative analyses also allow researchers to evaluate the results obtained by these traditional methods. All in all, Deloukas *et al.* suggest that they have annotated as many as 95% of the genes on chromosome 20.

The finished sequence and annotation¹ will be a boon to researchers interested in the diseases that have been linked to chromosome 20. The genes that cause Creutzfeldt-Jakob disease and severe-combined immunodeficiency (an autoimmune disease) were identified and mapped to chromosome 20 several years ago; the genes have since been well characterized.

But many other disorders caused by mutations in single genes or a variety of genes — including type 2 diabetes, obesity, cataracts and eczema — have also been linked to this chromosome. Although the exact genes have not yet been identified, the complete sequence will be invaluable, particularly as researchers have unlimited access to, and are able to freely use, the data. Even while the draft genome sequence was being generated, the discovery of several disease genes linked to chromosome 20 — including those that underlie Hallervorden-Spatz syndrome⁸ (a nerve-degeneration disorder) and Alagille syndrome⁹ (which is characterized by narrowing of the vein leading to the lungs) — was accelerated because the data were freely available. This was one of the goals of the public project from the beginning, and has meant that scientists have also been able to study several forms of cancer associated with chromosome 20. Of course it may take years, but identification of the disease-associated genes should lead, eventually, to a better understanding of the processes that lead to disease, and perhaps to treatments.

Another of the consortium's agreements¹⁰ was that the sequencing of each chromosome would be finished to the same high standards. These standards have been

met for all three completed chromosomes. Although draft data, even at low quality, are useful for initial gene identification and genomic studies, further sequencing and experiments are needed for more precise analyses. It took close to a year to convert the draft data of chromosome 20 to the finished sequence now published. The effort required to polish the last 5 megabases of draft data — and to close 38 of the 42 gaps in the sequence — is comparable to what was required to produce the entire draft. This highlights the fact that 'finishing' has many difficulties, both technically as well as in assessing whether the entire sequence has been covered and the data are of high enough quality.

Finishing includes a tedious process in which incorrect and ambiguous sites in the draft, even those as small as one base, are identified and corrected. Errors such as this have proven recalcitrant to automated sequencing processes, making it clear that the more laborious 'clone-by-clone' approach to finishing is a necessity (as opposed to the whole-genome shotgun approach used by Celera to obtain its draft data⁵). As a good example of this, the highest peak of G+C bases along chromosome 20 occurs at a different position in the finished chromosome 20 sequence¹ and in Celera's draft data⁵. (G+C-rich regions are often difficult to sequence and are of interest because they tend to contain more genes.) There are also major discrepancies between the public consortium's draft⁴ and finished¹ data for chromosome 20 (Fig. 1) — probably due to large duplications in the genome. As

pointed out by Deloukas *et al.*¹ (see Fig. 2 on page 868) and previously^{4,5}, the human genome contains many of these duplications, which might provide the raw material for the emergence of new genes during evolution in higher primates, including humans. Without clone-map information, it is hard to work out where duplicated segments fit in.

As with the Harry Potter series, we already know how long the complete works of the human genome will be — 24 instalments — and we can't wait to get our hands on them all. We have already had a few glimpses of what's to come, but there are many mysteries and secrets yet to be revealed. It's been a long wait between instalments two and three, but there should be a flurry of activity over the next year and a half; we expect the book of human genes to be wrapped up in spring 2003. ■

Masahira Hattori and Todd D. Taylor are in the Human Genome Research Group, Genomic Sciences Center, RIKEN Yokohama Institute, 1-7-12, Suehiro-cho, Tsurumi-ku, Yokohama, Kanagawa 230-0045, Japan.
e-mails: hattori@gsc.riken.go.jp
taylor@gsc.riken.go.jp

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Biomechanics

Damper for bad vibrations

R. McNeill Alexander

Some muscle fibres in the legs of horses seem to be evolutionary leftovers with no function. But in fact they may act to damp damaging vibrations generated in the leg as the horse runs.

Horses¹ and camels² have muscles in their legs with tendons more than 600 millimetres long connected to muscle fibres less than 6 millimetres long. Such short muscles can change length only by a few millimetres as the animal moves, and seem unlikely to be of much use to large mammals. The tendons function as passive springs, and it has been assumed that the short muscle fibres are redundant, the remnants of longer fibres that have lost their function over the course of evolution. But Wilson and colleagues argue, on page 895 of this issue³, that these fibres might protect bones and tendons from potentially damaging vibrations.

For mammals and birds with masses greater than a few kilograms, tendon elasticity substantially reduces the energetic cost of

running⁴. In humans, the Achilles' tendon is the principal tendon involved. In animals, other tendons in the lower leg are also important. Each time a foot hits the ground, these tendons are stretched. As the foot leaves the ground again, the tendons recoil elastically. Kinetic and gravitational potential energy are stored as elastic energy in the tendons and returned in the elastic recoil. Similarly, the kinetic energy lost by a bouncing ball when it hits the ground is also stored as elastic energy and returned in the recoil. So running animals effectively bounce along, using less energy than would be needed if their tendons were not elastic.

Compared with other tendons, such as those of the muscles that bend the joints of the leg, the energy-saving tendons have much