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NEWS

The sequencing of the rat genome

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Introduction

The sequencing of mammalian genomes continues apace. The common laboratory rat, *Rattus norvegicus*, is the third mammal after man and mouse to have its genome fully sequenced. The process and preliminary findings have recently been reported in detail.[1] As this multidisciplinary and international programme proceeds, we begin to see new patterns in the evolution of mammalian biology, not least in the development of genes closely involved in the development and defence against disease. The major contribution that unsung generations of rats have made to medical and oncological research now extends into the virtual digital world of genomic databanks and comparative genomic analysis.

The technical methodology and achievements of mammalian genome sequencing have been described elsewhere. They represent a continuing tour de force of meticulous analysis of DNA base sequence of huge numbers of gene fragments, and the assembly of these fragmentary sequences into a complete genome. The competitiveness which marked the race to the human genome between the private Celera corporation and the public institutions appears to have been replaced by a more cooperative strategy. Further genomes of mammals of importance to man, not least those of the great apes, are currently in the pipeline.

The physical structure of the rat genome

At 2.75 Gigabases (GB), the rat genome is only slightly smaller than the human genome (2.9 Gb) and larger than the mouse genome (2.6 Gb). The rat has 21 chromosomes, unlike mouse (20) and man (23). All three genomes code similar numbers of genes, around 30,000, most of which have persisted without significant change, duplication or deletion over 25 million years, where they can be traced to a common ancestor of the rat and mouse. Some 40% of the rat genome aligns very closely in structure and function with man and mouse, and a further 30% with the mouse. Some 10% of genes appear to code for structure and function specific to the rat, including immunology, pheromones and protein metabolism.

Huge computational power and sophisticated algorithms allow vast amounts of detailed and comparative data to be abstracted from the genomes on an individual base by base analysis. This data includes, for example, the areas of the genome with particularly high rates of evolutionary mutational change, and areas of inclusion of retroviral DNA into the genome, which accelerates the rate of genomic evolution over many generations.

Applications of the genomic data

Knowledge of genomic sequences does not in itself advance understanding of the function or structure of biological molecules, cells or organisms, for

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which the proteome, or totality of genomic protein product, is more important. However, genomic comparisons allow significant deductions to be made about the function of genes and their protein products, and interspecies differences. From a clinical perspective, the study of genes closely associated with human diseases may reap practical benefits, as the rat model allows effective experimentation over many generations and inbred strains.

There are now more than 1000 documented human hereditary diseases for which the underlying genomic disturbance is understood. Of these, some 75% have analogous genes in the rat. As with the fruit fly and the mouse genome, the new genomic sequence data and the surging advances in bioinformatics and organism biology which we continue to report[2-4] will permit methodical analysis of the effects of many mutations on growth, behaviour and disease, and their correction. The oncological applications of this new knowledge base have yet to be properly explored and developed, and there are unlikely to be practical spinoffs in the clinic for a long time to come. The rat has been the harbinger of plague and pestilence to man for millenia, and we can but hope that the huge investment in this project will help redress the balance.

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