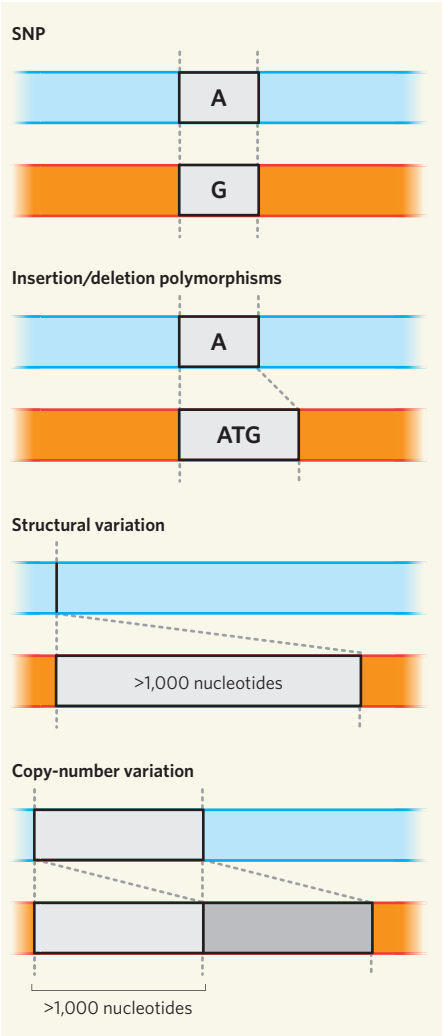

Figure 1 | Genomic variations. The latest whole-genome sequences of two humans confirm[4,5] that individual genomes vary in several respects. The types of variability in inheritance include: variations in single nucleotides (SNPs); insertion or deletion of several nucleotides; insertion or deletion of thousands of nucleotides (structural variation); and duplication or multiplication of DNA segments more than 1,000 nucleotides long (copy-number variation).

latest approach is the extent of deep sequencing achieved, which aids SNP identification.

The advantages of obtaining these two genomes, such as the identification of DNA variations, indicate that their usefulness will ultimately be much broader than simply demonstrating the technological milestone of relatively low-cost sequencing. But some goals remain. As the genomes were reconstituted on the basis of alignments with existing reference genomes, the set of non-SNP variants that are absent in the reference genome will be incomplete. For example, in these studies, the detection of structural variants — insertions or deletions of thousands of nucleotides at any one position on a chromosome — is preferential for deletions. This is because such insertions come from sequenced reads that will not overlap with the existing reference genome. There are two possible solutions to this detection bias. One would be to sequence larger DNA fragments whose ends overlap with sequences on the reference genome[8]. Alternatively, all sequenced reads could be assembled independently, before mapping them to a reference human genome[6].

Another deficiency of the four genomes[4–7] is that they do not accurately define copy-number variants at the nucleotide level. These forms of genetic variation arise from the insertion of multiple copies of DNA segments that may include whole genes and that have been increasingly implicated in, among other disease phenotypes, neurological disorders[9,10].

Our genomes are not just collections of DNA variation: parental inheritance also dictates specific associations between neighbouring variations. Knowledge of these associations will ultimately help us discover whether and how much of an aberrant protein is produced by each of our cells and how these events contribute to observed phenotypes. The association between neighbouring variations across all 23 pairs of human chromosomes is referred to as haplotype assembly, and has not yet been completely achieved in any of the individual genomes sequenced.

These limitations notwithstanding, the approach of Bentley[4], Wang[5] and their colleagues represents a substantial advance in the sequencing of individual human genomes. Together with the other two genomes sequenced[6,7], they reinforce the catalogue of variants that exist in human genomes — SNPs in the millions, insertion/deletion polymorphisms in the hundreds of thousands and structural variants in the thousands. The numbers of these variants do not directly tell us how such polymorphisms contribute to the wide spectrum of human traits. But they do provide a necessary step towards accurately defining genomic loci that are likely to be implicated in those traits.

With such rapid advances in next-generation technologies, and with 'third generation' technologies emerging, this is just the beginning of the era of the individual genome. Soon, association studies using complete individual genomes will become the approach of choice for understanding the complexity of human biology and disease. The latest advances have broad implications for expediting that goal. ■

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50 YEARS AGO

Nobel Prize for Chemistry:
Dr. F. Sanger, F.R.S. — The award has been made for his researches on the structure of the protein hormone insulin ... When he began his investigations on insulin, Dr. Sanger first devised the use of dinitrofluorobenzene for the identification and estimation of the free amino-groups of proteins or peptides, and this method has since been widely adopted ... Dr Sanger's methods and example have stimulated much research in the investigation of protein structure, the limits of which have yet to be visualized, and they make clear the possibility that insulin may be completely synthesized in the laboratory, although this is unlikely to occur for some time to come.
From *Nature* 8 November 1958.

100 YEARS AGO

Windmills and Water-Wheels.
By R. S. Ball — As is natural, the author commences his book with a reference to the, said to be, not distant day when all the coal, and all the oil, in the world will have been used up, and mankind, in order to sustain itself, will have to rely wholly upon the water-wheel and the windmill for that tremendous amount of energy which will be necessary to keep the immense population of the earth in the state of comfort which it has, with the progress of civilization, attained.

ALSO:
A meeting of the Child Study Society was held on October 29, when a paper was read by Miss Alice Ravenhill on the results of an investigation into hours of sleep among elementary-school children ... The evil of insufficient sleep is widespread. Parents must be roused to a sense of the importance of the subject, and the enforcement of the laws on the employment of children should be rendered obligatory upon local authorities.
From *Nature* 5 November 1908.

50 & 100 YEARS AGO