EDITORIAL

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Strange Case of Dr. Watson and Mr. Venter

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In the famous novella written by Robert Louis Stevenson more than a century ago, **Strange Case of Dr. Jekyll and Mr. Hyde**, a lawyer investigates bizarre events related to his friend Dr. Henry Jekyll and the cynic Mr. Edward Hyde. The work captures a subtle portrayal of a person displaying a split identity. While this rare mental disorder shows nowadays a sharp rise in incidence across continents and might constitute the topic of our editorial, the question arises – what else makes us to investigate here the Case of Dr James Watson and Mr Craig Venter?

First, our main characters are two magnificent scientists of our time and their contribution to human genetics [1,2] is probably not enough acclaimed. A noticeable reward, however, might be the fact that **Watson and Venter are the first two humans having their genome fully sequenced** [3,4]. This recently published work follows the heroic era of the Human Genome Project [5], which culminated with the ultimate meaning of the information age: the alphabet of the human health. Soon after this revolutionary accomplishment, it became clear that the definitive answer to the question – what are we to make of it? implies the sequencing of individual human genomes. For a couple of years the two available versions of the human genome were products of the Human Genome Sequencing Consortium [5] and Celera Genomics [2]. They were derived from clone-based and whole-genome shotgun sequencing strategies, respectively. The Human Genome Sequencing Consortium assembly is a composite derived from numerous donors, whereas the Celera version of the genome has been collected from only five individuals. Both versions almost exclusively report DNA variation in the form of single nucleotide polymorphism (SNPs).

What about the technology behind genome sequencing of individual humans? In their effort to decrypt Dr Watson's base pairs, Wheeler and collaborators [3] used new DNA-sequencing platforms marketed by 454 Life Sciences, a division of Roche Diagnostics [6]. These instruments achieve massive parallelization and employ methods radically different than those used within the Human Genome Project. While the efficiency of biochemical and measurements steps is considerable, **the analysis of the data strongly depends on the high-quality reference sequence produced by the Human Genome Project**. The other team, which succeeded in analyzing Mr Venter's genome [4], used a standard, whole-genome shotgun sequencing strategy.

What about the cost? The development of new methods aiming to drive the cost of sequencing of an individual human genome to below $1000 is a key topic in personal genomics and medicine [7]. Although the cost has not attained this democratic level with the commercialization of novel DNA-sequencing platforms, **the price for decoding Dr Watson's genome is estimated at one million of dollars**, meaning cca. 1% of the funds involved in the Human Genome Project.

Who is the cynical one, Dr Watson or Mr Venter? This essential question has been formulated in the **News and Views** section preceding the article of Wheeler and colleagues [3] – **what can we expect to learn from the sequences of individual genomes?** The answer is rather depressing, in the sense that **the main lesson is that it will be extremely difficult to extract medically, or even biologically, reliable inferences from individual sequences**. The major difficulty is illustrated by the comparison of these recent results with the reference human genome sequences. The analysis revealed, in both studies, that the majority of genomic alterations are the well-studied class of variants based on SNPs. In particular, Wheeler *et al.* have found more than three million SNPs in Watson's genome relative to the Human Genome Project reference sequence! More than ten thousands of Watson's SNPs are expected to change the function of a protein and an unknown number of additional SNPs likely affect the regulation of protein levels. Accordingly, if the proteins of any two individuals are compared in detail, a significant fraction will be found to differ. In only few, peculiar cases possible biological effects arising from these differences could be inferred.

What's Next? Until now, large-scale studies of human genetic variation have focused mainly on understanding the pattern of SNPs. However, recent studies, that have identified larger polymorphisms (such as insertions, deletions or inversions), have also emphasized the need for more comprehensive and systematic studies of human structural genetic variation. The challenge has been taken and the first high-resolution

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sequence map of human structural variation has just arrived! Eichler and colleagues [8] have implemented an approach to construct clone-based maps from eight human genomes of diverse geographic ancestry and have succeeded in systematically sequencing structural variants more than 8 kbp in length. Among other surprises, they discovered few hundred new insertion sequences that are not present in the human reference genome. Moreover, these insertion sequences are variable in copy number between individuals. These findings represent a prelude to future individual genome studies, and more generally, to the central goal in human genetics of correlating genotype with phenotype, with special attention to disease predisposition and response to therapy. In this context, the **Personal Genome Project** [9], introduced at the beginning of 2006, aims to publish the complete genomes and medical records of several volunteers in order to enable research into personalized medicine. Specifically, the resources will include besides full genome sequences and digital medical records, other relevant information such as comprehensive data about RNA and proteins, body and facial measurements, and MRI and other cutting-edge imagery. Personal genomics remains a land full of promises! Yet, the actual practice of personalized medicine will have to wait until one can make reliable predictions from individual genome sequences… Thank You Lord, we are stranger than Dr. Jekyll and Mr. Hyde!

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