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THE GENOME

The sequencing of the human genome at the beginning of the twenty-first century represented a landmark achievement of biomedical science. Since then, the rapidly declining cost of sequencing, the burgeoning computational capacity to mine the ensuing data, and the expanding toolkits to analyze functional outputs (genomics, proteomics, and metabolomics) promise to revolutionize our understanding of health and disease. The emerging information has also revealed a breathtaking level of complexity far beyond the linear sequence of the genome. The potential of these powerful innovations to explain disease

pathogenesis and drive therapeutic discovery excites and inspires scientists. The human genome, with its 3.2 billion DNA base pairs, is a vast and complex system. Yet, with the genome, there are only about 20,000 to 25,000 protein-encoding genes. The number of encoded proteins (many genes produce multiple RNA transcripts that translate to different proteins) is nevertheless startling to realize that worms, which have only 1000 cells and have 30-fold smaller genomes, also have about 20,000 protein-encoding genes. Many of these proteins are recognizable homologs of molecules expressed in humans. What then separates humans from worms? The answer is not completely known, but evidence suggests that much of the difference lies in the 98.5% of the human genome that does not encode proteins. The function of such long stretches of DNA (so-called genome "dark matter") was mysterious for many years. However, over 85% of the human genome is ultimately transcribed, and nearly 80% is devoted to regulation of gene expression. It follows that while proteins provide the building blocks and machinery required for assembling cells, tissues, and organisms, it is the noncoding regions of the genome that provide the critical "architectural planning." Practically stated, the difference between worms and humans apparently lies more in their genomic "blueprints" than in their construction materials.