

RENAISSANCE OF SICKLE CELL DISEASE RESEARCH IN THE GENOME ERA



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### Foreword

### by Francis S. Collins and Alan E. Guttmacher

The "genetic era" might be said to have begun in April 1953, with Watson and Crick's description of the DNA double helix. Sickle cell disease earned an historic distinction in this newly born era with Ingram's description in 1957 of the first molecular basis for a disease, the substitution of valine for glutamic acid at the sixth position of the beta-globin chain, as the cause of sickle cell disease. This knowledge of its genetic nature contributed to many advances in our understanding of the biology of sickle cell disease, such as the pathophysiological importance of hemoglobin polymerization. However, despite the historical prominence of sickle cell disease in genetics, genetics-based knowledge has thus far led to only modest progress in prevention and treatment. Sickle cell disease continues to be a significant cause of morbidity and mortality, both in the United States and globally.

Exactly half a century after Watson and Crick's publication, the "genome era" began with the Human Genome Project's production of the finished sequence of the human genome in April 2003. Will prevention of and therapy for sickle cell disease fare any better in the genome era than in the genetic era? That crucial question is, in many ways, the focus of this volume, which reviews the history of our social and biomedical understanding of sickle cell disease, details our current state of knowledge, and highlights promising areas for future discovery.

There are a number of reasons to be optimistic that the tools and approaches of genomics will, indeed, significantly advance our understanding of sickle cell disease and provide more effective clinical strategies that improve the lives of individuals and families with the condition. The genetic era, with its focus on single genes and how they function, provided important knowledge. The genome era, with its focus on all of the 20,000 or so genes in the human genome, should provide much richer and more clinically relevant understanding.

For instance, those who are members of families with sickle cell disease, or have cared for individuals with the disease, see daily proof that the expression of the same single nucleotide substitution can cause widely varying effects in different individuals. Why is this? Genomics should help tell us.

We know that different variants nearby the *HBB* gene, particularly affecting fetal globin expression, can translate into different levels of severity. However, much more is involved in the varied health of those with sickle cell disease than variants in this gene cluster alone. Clearly, the *HBB* gene

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interacts both with multiple other genes and with environmental factors, and it is these complex, and hitherto mysterious, interactions that determine health impact. Such tools of the genome era as genome-wide association studies, high throughput sequencing, and sophisticated bioinformatics should enable, for the first time, the identification of important modifier genes and gene-environment interactions, and thus help to unravel this crucial mystery.

Moreover, modern genomic approaches offer optimism not just for improved understanding, but for improved therapies. For instance, the combination of high throughput technologies, easily accessible libraries of hundreds of thousands of small molecular compounds, and the human genome sequence's supply of new targets, make "chemical genomic" approaches practical ways to develop novel therapies for such previously intractable clinical problems as sickle cell disease.

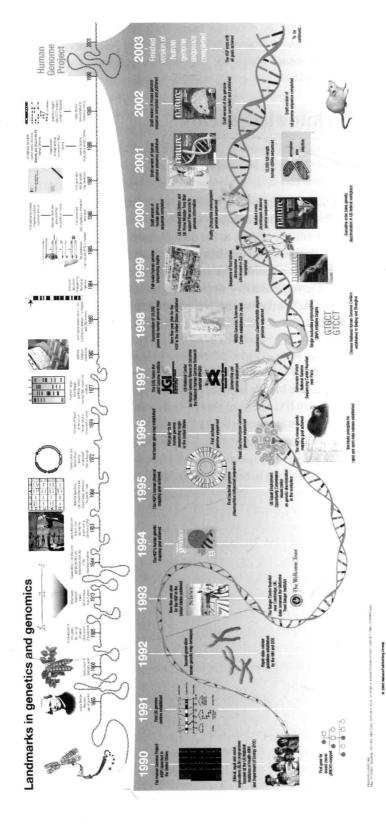
One advantage of the genome era should be that it can profit from the sometimes hard-won lessons of the genetic era, if we are only wise enough to learn from them. Sickle cell disease is distinctive in genetics not only for its preeminence as a molecular model of disease, but also for its sobering reminder that the application of genetic science can inflict discriminatory injuries upon individuals, families, and communities living with genetic disease. These lessons have been heeded, and the genomics era has been truly informed, even shaped, by the social and ethical lessons of sickle cell disease research in an earlier time. As a consequence, genomics may indeed be unique among areas of biomedicine for having, almost since its inception, included a focus on ethical, legal, and social implications (ELSI) issues. This sensitivity includes the conclusion that truly effective biomedical research must involve active participants who help shape the research agenda and delineate its features, rather than passive "subjects" on whom research is done. We believe that this attention to ELSI issues is another important genomic principle, one that should play a vital future role in shaping both basic science and applied biomedical approaches to sickle cell disease.

The Human Genome Project has already proven to be a milestone in the history of biology. However, for the genome era to be an equally important milestone in the history of medicine, it must prove that it can lead to important advances in health. We look forward to the path forward discussed so ably in this volume, turning the great promise of the genome era into a reality of better prevention and treatment of sickle cell disease.

Francis S. Collins Alan E. Guttmacher

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# A Vision for the Future of Genomics Research

In contemplating a vision for the future of genomics research, it is appropriate to consider the remarkable path that has brought us to the genome era. The rollfold shows a timeline of landmark accomplishments in genetics and genomics, beginning with Gregor Mendel's discovery of the laws of heredity material (1866) and their rediscovery in the early days of the twentieth century. Recognition of DNA as the hereditary material (1944), determination of its structure (1953), elucidation of the genetic code (1966), development of recombinant DNA technologies (1972) and establishment of increasingly automatable methods for DNA sequencing in the seventies, made it possible for the Human Genome Project to begin in 1990. The creativity and determination of a legion of talented scientists made this project a success and set the stage for a revolution in biological research. Use by permission from FS Collins, ED Green, AE Gutmacher and MS Guyer, Nature 422, 835–847, 2003. Larger image available at www.genome.gov/11007524.