Preface

This is not a typical book about genomics, evolution, and molecular medicine where you are provided with comprehensive information reinforcing what you already know. Rather, this book will invite you to rethink the fundamental theories of genetics and evolution you have held for so long—knowledge that has formed the style of your scientific thinking and practicing and that has sculpted you into who you are today.

Perhaps you are an undergraduate student or a fresh graduate, younger than the age of genomics, who grew up amid large-scale -omics technical platforms and promises. You dreamed of becoming a hero by finally curing cancer in the age of big data and personalized medicine. "Is this necessary?" you may wonder.

Or perhaps you are established in the field. "Why bother?" you may ask. "Why do we need to reexamine the frameworks in a blossoming field such as genomics and molecular medicine? We have headline after headline trumpeting the success of the Human Genome Project and many the large-scale -omics projects that followed." Your career is going well; you are widely published, well-funded, and respected. "Yes, there are many big surprises," you argue, "but science is naturally a half-full or half-empty story. The logical way to advance the field is by continuing to improve technologies to collect more data. With more funding, the mystery of life will be solved, and all diseases will be eradicated."

After reading report after report on the major failures of molecular targeting-based clinical applications or after witnessing the disappointment of large-scale genome-wide association studies or after the cancer genome project bluntly questions the value of your personal research (when the list of the top 100 most mutated genes in cancer does not include your favorite gene), occasionally, in the back of your mind, you might have asked yourself, "Geez, how did we miss it again? So many years of hard work and experimentation had clearly already proved the importance of this gene mutation in cancer."

Then came a series of shocking and nerve-racking report: most landmark studies in oncology (nearly 90%) are unrepeatable. The success rate of translational research is extremely low, akin to "crossing the valley of death." "Genomics is good for research, but not for medicine." "Current US biomedical research needs to be rescued from its systemic flaws."

These conclusions are based on solid analyses and can no longer be ignored. How does one reconcile positive and negative news in the

genomic era? What are the key implications of these surprises? How should the fields of genomics and molecular medicine move forward? And more profoundly, do those stunning reports reflect the increased anomalies and paradoxes that are crying out for a paradigm shift in biomedical research?

In this book, these issues will be systematically and candidly discussed. In particular, you will be introduced to a different conceptual framework of biological reasoning, exposing holes in traditional ways of thinking and conducting research. By reexamining many paradoxes through the lens of the genome theory, rather than the gene theory you are so familiar with, this book will lead you to discover a new way to appreciate how genomics and evolution work in the context of heterogeneity/emergence-defined reality. Perhaps you will realize that many well-known milestone findings in classic genetics and evolution are in fact less important as they represent exceptions rather than generalities. These new "discoveries" and further syntheses, many of which may initially seem counterintuitive and controversial, will surely challenge your own knowledge and beliefs. At the start, they may make you uncomfortable. But hopefully, at the end of the day, many of these proposed concepts and statements will make sense to you.

We explore this paradigm shift in eight chapters:

In Chapter 1, "From Mendelian Genetics to 4D Genomics," a brief review of the birth of genomics and its relationship with the Human Genome Project is presented, which illustrates how the concept of the gene has changed during the genomics era. Further discussions highlight some key limitations of traditional genetic/genomic research and call for a new genomic paradigm.

Chapter 2, "Genes and Genomes Represent Different Biological Entities," supports the concept that the emergent genome, rather than isolated genes, defines a biosystem. Many gene-centric concepts and their limitations are briefly reviewed. Experimental observations are presented to illustrate the conflicting relationship between genes and the genome, as the genome-level operation is not simply a matter of "adding up" the functions of individual genes.

Chapter 3, "Genome Chaos and Macrocellular Evolution: How Evolutionary Cytogenetics Unravels the Mystery of Cancer," discusses why a new conceptual framework of cancer research is urgently needed and describes the journey of searching for a genome-based cancer evolutionary theory. This journey has led to many important discoveries, including two-phased cancer evolution (macro- and microcellular evolution), the importance of nonclonal chromosome aberrations, the key function of genome chaos, and the evolutionary mechanism of cancer. A new genomic model for cancer evolution is proposed to relate the contributions of genome and gene in cancer evolution.

In Chapter 4, "Chromosomal Coding and Fuzzy Inheritance: The Genomic Basis of Bio-information and Heterogeneity," the many genomic surprises observed from the first three chapters are explained by the novel concepts of system inheritance and fuzzy inheritance. Unlike gene-defined "parts inheritance," chromosome-encoded "system inheritance" defines the genomic blueprint. In addition, the multiple levels of genomic and nongenomic information are fuzzy, which allows them to code for a spectrum of potential genotypes for the environment to select. Furthermore, fuzzy inheritance is the genomic mechanism of bio-heterogeneity, which is the key to understanding many common and complex diseases.

In Chapter 5, "Why Sex: Genome Reinterpretation Dethrones the Queen," an unexpected story likely solves the century-long mystery behind the main function of sexual reproduction, the "queen of problems" in evolutionary biology. Initially, the two phases of cellular evolution suggested that asexual reproduction can produce highly diverse genomes, whereas sexual reproduction should produce identical genomes. Ample evidence from different organisms now supports this new concept. Furthermore, meiosis has been identified as the mechanism to maintain species identity by preserving system inheritance. Thus, the primary function of sex is to preserve the genome-defined system (the species).

In Chapter 6, "Breaking the Genome Constraint: The Mechanism of Macroevolution," following a brief review of the fundamental differences between artificial selection, highly isolated natural selection, and natural selection in general, the maintenance of genome integrity is linked to major evolutionary constraints. After emphasizing the importance of evolutionary constraint, a new model of speciation is proposed. In this model, speciation is characterized by genome reorganization-mediated macroevolution, mating with a partner of a similar genome to produce fertile offspring. Finally, microevolution might promote the formation of lasting species with large populations. This model drastically departs from the explanation of speciation through natural selection, where the accumulation of the small changes over long period of time is key.

In Chapter 7, "The Genome Theory: A New Framework," the rationale for integrating genome-based genomics with evolutionary concepts is laid out alongside the key assumptions that validate them (treating the genome as an information unit, evolutionary selection unit, and platform of bio-emergence). The genome theory is cohesively outlined with 12 principles. In addition, the genome theory's key predictions and limitations, as well as its falsifiability, are discussed.

In Chapter 8, "The Rationale and Challenges for Molecular Medicine," the history of precision medicine, as well as its challenges and opportunities, is briefly traced. The future direction of molecular medicine is discussed, including the relationship between big data and theory,

the increase in bio-uncertainty, and how education can play an important role in the future of biomedical science.

Although the chapters are arranged in a logical order that reflects our journey of thinking and searching, each chapter has been written as a potential standalone unit for the ease of readers. Therefore, there is some minimal overlap among chapters. The commonly shared message that threads all eight chapters together is the importance of genome-defined genomic information and its implications for evolution and molecular medicine. More specifically, the often-ignored role of genome constraint in evolution is emphasized. Within this new perspective, both the system's variable features (reflected as short-term adaptive dynamics) and the existence of the system itself (reflected as long-term stasis) are essential components, marking a departure from current genomic and evolutionary theories. Such new theories based on real-world complexity will not only challenge current genomic and evolutionary mechanisms, but also explain the relationships between micro-adaptation and macro-speciation, germline stability and somatic dynamics, and fuzzy inheritance encoded phenotype potentials and environment-selected realities.

By analyzing initial confusions, identifying paradoxes, thoroughly reinterpreting key data, rethinking ignored phenomena, introducing new discoveries, and searching for new frameworks, this book invites you to join us on this journey of rediscovery. If you are a genome-based reader, help us to improve the genome theory and establish a technological platform to study human diseases. If you are a hard-core gene-based reader, bear with us and momentarily set aside the ideas you know best to have a conversation about ideas that you may have dismissed, ignored, or even disliked. We are always searching for a better theory, after all. Maybe you will come up with a strong argument to convince us to join you.

No matter what, the only goal of a true scientist should be to search for truth. In that light, I hope this process, no matter how difficult, will be enjoyable. Sometimes the truth hurts. Often, it is not easily appreciated, especially when an improper framework has previously dominated our thinking. But ultimately, truth will prevail. When you finish reading and ponder our message, you will likely start to ask a few questions. "Is this really real?" you may wonder. And "If so, how did I miss something this big for so long?" And hopefully, "What should I do next?"