From Genes to Genomes

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Genome Chaos: Rethinking Genetics, Evolution, and Molecular Medicine
by Henry Heng
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Genome Chaos is a book of no small ambition. Based on his experience in cancer cytogenetics, Henry Heng invites readers to rethink the role of the genome in determining the hereditary properties of cells and organisms. He distinguishes between gene-centric and genome-based views of heredity and argues that the physical organization of the genome incorporates a higher systems level of information beyond its genes or coding sequences. For Heng, genes are rather like a parts list capable of encoding proteins and RNA that can be assembled and used in many different ways to produce cells and organisms with quite distinct properties. In making his argument, Heng challenges a number of notions about the genotype–phenotype relationship.

According to Heng's genome-based perspective, evolution can be broken down into two modes. Microevolutionary change operates within species much as Charles Darwin envisaged, by "numerous, successive, slight modifications."[1] Macroevolutionary change rapidly restructures the genome to establish a new architecture, leading to new species and new phenotypes without changing the basic gene content. The transition from microevolutionary to macroevolutionary change—the period Heng labels *genome chaos*—occurs when there is great stress on either somatic cells, as in cancer chemotherapy, or independent organisms, as in episodes of drastic ecological change and mass extinctions.

These ideas are not completely new. In 1940, Richard Goldschmidt distinguished between micro- and macroevolutionary processes in *The Material Basis of Evolution*.[2] Later in that decade, Barbara McClintock described processes involving rapid genome reorganization.[3] Heng's approach is novel because it is based largely on his extensive cytogenetic research in somatic cancer cell evolution. He observed that when tumor cell populations undergo major transitions—benign to malignant, localized to metastatic, and drug-sensitive to drug-resistant—the vast majority display major karyotype changes. For a period, non-clonal chromosomal aberrations (NCCAs) appear and disappear among the tumor cells until a relatively stable population emerges with a new growth phenotype and a karyotype displaying clonal chromosome aberrations (CCAs). The period of NCCAs is the time when macroevolutionary karyotypic changes occur leading to a series of novel genome architectures until one or more of them produce the appropriate phenotype for stable tumor cell propagation under the new conditions. In Heng's concept, it is the genome system properties of novel chromosome organizations and not specific gene content that drives the major steps in the evolution of all but a few exceptional cancers.

A chapter of *Genome Chaos* is devoted to applying these conclusions to organismal evolution. A similar model, Heng claims, fits the punctuated nature of the fossil record and cytological observations of chromosomal differences within groups of closely related species.[4] Chimpanzee and hominid gene sequences match to within 98%, but they differ with respect to a chromosome fusion and several inversions. The result is that chimpanzees (2n = 48) have a karyotype with two more chromosomes than hominids (2n = 46). Similarly, primates and rodents share more than 99% of their proteins yet have radically different karyotypes and developmental trajectories (for the mouse, 2n = 40).

Heng's idea that genome system information is critical in taxonomic divergence has some interesting implications, notably the counter-conventional notion that the normal evolutionary function of sexual reproduction is to suppress, rather than enhance, major phenotypic variation within species. The need for meiotic chromosome pairing in the formation of gametes at each generation prevents individuals carrying germline chromosome changes from producing progeny who can pass on those changes.[5]

The most controversial aspect of Heng's argument in *Genome Chaos* is the claim that specific gene-based changes play a minor role in the macroevolutionary process. Heng points out that Gregor Mendel based his laws of inheritance on a few selected markers with high phenotypic penetrance. Observable Mendelian patterns of

inheritance are the exception rather than the rule for single-gene alterations. Heng describes the absence of a strong, predictable consequence of single gene mutations as fuzzy inheritance. Single-gene changes evoke a weak effect because most organismal phenotypes result from the complex interaction of elaborate cellular networks, sensitive to both internal and external conditions. While a particular protein or RNA may participate in various networks, most major adaptive features of complex organisms are robust to defects in any single molecular component of those networks. Heng repeatedly emphasizes the importance of variability and heterogeneity for biological systems, features which clearly distinguish them from nonbiological systems.

Only a very small number of tumors, Heng observes, generally blood cancers, can be explained as the result of changes at specific genetic loci, either cancer-stimulating oncogenes or cancer-inhibiting tumor suppressor genes. He argues that the inherent complexity and heterogeneity of biological systems dooms currently popular genome-wide association studies to identify particular gene mutations that determine cancer progression. At best, they can only assign a very small fraction of heritability to specific genetic loci in the majority of cancers. The same analytic weakness is true of many heritable human diseases, again with a small number of highly penetrant exceptions, such as sickle cell anemia. According to Heng, the focus on individual genes in human disease means that the genome's karyotype system information is overlooked. This information is inherent to the chromosome configuration of the particular cancer or tissue somatic cell. Trisomy 21, causing Down syndrome, is a very simple example of the importance of karyotype system information. It is also an illustration of inherent phenotypic heterogeneity, which is reflected in the broad range of severity in the development disorders observed in individual Down syndrome cases.

At numerous points throughout *Genome Chaos*, Heng urges researchers to reorient their thinking about basic evolutionary processes. He argues persuasively for a shift from a gene-based to a genome-based approach, a transition he describes as moving from a one-dimensional to a four-dimensional view of genomic information and function. The potential impact of such a transition highlights the many challenges arising from Heng's proposal of a central role for karyotype change in both organismal and cancer cell evolution. Researchers do not yet understand the phenotypic effects of chromosome reorganization at either level. It is not even clear how we might specify the role of the individual components that make up genome system information. We do know some of the molecular and cellular features involved in determining the karyotype–phenotype relationship: the formatting of genomic chromatin domains, intra- and interchromosomal contacts between transcriptional regulatory motifs, the establishment of topologically associated domains and transcription factories, and the existence of subnuclear compartments. Yet there is no comprehensive theory that accounts for how a given genome architecture facilitates the expression of particular phenotypes using the parts list specified by its coding sequences. Heng's argument effectively places researchers in a position comparable to that of the pioneers of genetics in the early twentieth century.

Cancer and evolutionary biologists currently lack a comprehensive understanding of genomic chaos. Nonetheless, we are beginning to learn from whole genome cancer data about specific features of genomic chaos, such as the effects of changes in mobile repetitive DNA.[6] Moreover, we also know that stress and crisis trigger massive restructuring of cancer cell karyotypes, and there has been promising research on the role of cell fusions and chromosome-scrambling non-mitotic cell divisions by polyploid giant cancer cells in these sudden and massive genome structural changes.[7] Despite our current relative ignorance, we can reasonably expect that patterns will be discerned in the whole genome sequence data that will provide greater mechanistic insight into how chromosome restructuring episodes occur, with important implications both for cancer therapy and evolutionary biology.

The case Heng makes for thinking about genomes rather than just genes is strong and convincing. By alerting the genomics community to a new scientific frontier, *Genome Chaos* accomplishes two important and complementary goals. It clearly demonstrates that a great deal of fundamental evolutionary biology and genetics research still needs to be done before newly acquired genomics and genome-editing technologies can be used to maximum advantage. *Genome Chaos* also offers useful ideas about where research efforts and funding can be deployed most effectively.

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1. Charles Darwin, *Origin of Species* (1860), 189, in The Complete Work of Charles Darwin Online, ed. John van Wyhe (2002).
2. Richard Goldschmidt, *The Material Basis of Evolution* (New Haven: Yale University Press, 1940).
3. Barbara McClintock, "Maize Genetics," in *Carnegie Institution of Washington Year Book* 45 (1946): 176–86; Barbara McClintock, "Cytogenetic Studies of Maize and Neurospora," *Carnegie Institution of Washington Yearbook* 46 (1947): 146–

52; Barbara McClintock, "Mutable Loci in Maize," in *Carnegie Institution of Washington Yearbook* 47 (1948): 155–69.

4. Niles Eldredge and Stephen Jay Gould, "Punctuated Equilibria: An Alternative to Phyletic Gradualism, in *Models in Paleobiology*, ed. Thomas Schopf (San Francisco: Freeman, Cooper & Company, 1972), 82–115.
5. It is intriguing to recall in this context that sex *between* species has exactly the opposite effect—interspecific hybridization followed by whole genome doubling has been extensively documented as a reliable trigger for genome instability and rapid speciation. G. Ledyard Stebbins, "Catalysmic Evolution," *Scientific American* 184, no. 4 (1951): 54–59, doi:10.1038/scientificamerican0451-54.
6. ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium, "Pan-Cancer Analysis of Whole Genomes," *Nature* 578 (2020): 82–93, doi:10.1038/s41586-020-1969-6; Bernardo Rodriguez-Martin et al., "Pan-Cancer Analysis of Whole Genomes Identifies Driver Rearrangements Promoted by LINE-1 Retrotransposition," *Nature Genetics* 52 (2020): 306–19, doi:10.1038/s41588-019-0562-0.
7. Ivan Shabo et al., "Roles of Cell Fusion, Hybridization and Polyploid Cell Formation in Cancer Metastasis," *World Journal of Clinical Oncology* 11, no. 3 (2020): 121–35, doi:10.5306/wjco.v11.i3.121.

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