Annual Review of Genomics and Human Genetics, 2012. Aravinda Chakravarti and Eric Green (eds). Annual Reviews, 4139 El Camino Way, P.O. Box 10139, Palo Alto, CA 94303-0139, USA. Vol. 13. 469 pp. Price: US$ 89.

The book under review contains 20 review articles contributed by 41 authors. It is a collection of a wide spectrum of contemporary topics on various aspects of genomics and human genetics, ranging from evolutionary and population genetics, genomics of complex and Mendelian traits, to the latest research on rapidly emerging fields of functional genomics, genomics of infectious diseases and metagenomics. A few chapters are also dedicated to the ethical and teaching-related issues. The editors deserve full credit for recognizing current thrust areas of genomics and inviting researchers of high repute to contribute articles.

The volume begins with the article by Maynard V. Olson on human genetic individuality. The author explains how genetic individuality is different from genetic variations present in individuals in this ingeniously drafted review. Olson has emphasized that while understanding the genetics of disease phenotypes is of utmost priority, significant effort should be dedicated to explore genomics of so called 'normal' phenotype. Evolutionary forces such as balancing selection and local adaptation have major implications mostly in genomics of infectious diseases, but the author states that, by and large, a combination of evolutionary mechanisms like mutation-selection balance and founder effects are responsible for genetic individuality. The concept of 'clan genomics' is well-articulated in situations where locus heterogeneity exists at an extreme level. Improved technologies of DNA sequencing are gradually shifting the focus from common variant common disease (CVCD) to individual rare genetic variants with large effect for 'missing heritability' in complex diseases. The author is more concerned about the implications for non-disease phenotypes and has concluded the article with a special note on the famous Dobzhansky–Muller debate on evolution of human phenotypic variation.

Both chapters 2 and 3 are excellent evaluations of methods related to discovery and functional characterization of DNA elements combining the traditional molecular biology techniques to decipher gene regulation at a genome-wide scale using high-throughput genome sequencing methods such as massively parallel sequencing. With recent completion of projects like ENCODE, researchers in this field would be immensely benefited from both these chapters. Chapter 2 deals with the role of enhancers globally and methods to characterize complex regulatory interactions, while chapter 3 specifically focuses on molecular techniques to identify higher-order chromatin structure. In the beginning of chapter 2, the authors provided useful and informative schematics of comparing multiple approaches used in genome-wide mapping of transcription factor (TF) sites. The chapter also has a detailed list of cautionary notes and examples of each technique described in this review. The authors have also briefly touched upon the system biology and computational components of gene regulation. Clear distinction of methods such as ChIP-on-chip or ChIP-seq (used primarily for discovery of TF binding sites) with ChIA-PET (chromatin interaction analysis through paired-end tag sequencing is mostly used to discover TF–DNA interaction), would give researchers an opportunity to design experiments according to their specific need. There is an elaborate discussion on genome-wide identification of open chromatin structures and DNA–DNA interaction sites in chapter 3. Transition of traditional long-range chromatin interaction methods like chromosome conformation capture (3C) to recently developed Hi-C or ChIA-PET with combinations of high-throughput deep sequencing methods has certainly made life easier for researchers engaged in investigating complexities of higher-order chromatin structure. Some important insights from chapter 2 such as (i) TFs do not bind to all binding sites in the genome, (ii) pioneer TFs can bind to nucleosome-wrapped sites despite chromatin assembly being a barrier for TF binding, (iii) apparently nonfunctional TF can also regulate gene expression at a later stage of development through its enhancer, etc. essentially indicate towards existing case-by-case variations in TF-driven gene regulation in biological systems.

Some chapters are devoted to genomics of complex human diseases, including cancer and metabolic diseases. Chapter 8 is an extensive review on genomics of hepatocellular carcinoma (HCC) with elaborately illustrated pathways involved. The author has pointed out the importance of identification and cataloguing driver mutations in HCC patients with diverse clinical features by thorough investigation of genome and epigenome in germline versus somatic conditions using high-throughput sequencing strategies which would eventually facilitate discovery of personalized genomic medicine for patients. On this note, it is worth mentioning that a consortium dedicated to cancer genomics (International Cancer Genome Consortium) is already engaged extensively to work on this strategy to be applicable in all cancer types. Another interesting article (chapter 9) has discussed a rare, transmissible form of facial cancer in an Australian marsupial, the Tasmanian devil. This is the only article in the book, focused on genomics of a non-human species. The Tasmanian devils are on the verge of extinction due to the facial tumour disease. The authors believe that a comparative tumour genome analyses with humans would help identify novel candidates, which may eventually lead to possible therapeutic outcomes to prevent this species from extinction. Chapter 10 deals with a huge public health burden of sudden cardiac arrest leading to death of individuals. The authors provided an in-depth review on genetic susceptibility of sudden cardiac death (SCD). Most candidate gene screening studies with a case-control design have identified novel, rare variants in SCD, but their mechanisms and relevance are not yet fully understood. Hypothesis-free genome-wide association studies (GWAS) have discovered many risk loci in SCD. The authors believe that strategies like GWAS are important in identifying high-risk individuals who require immediate medical intervention. Chapter 11 on genetics of substance dependence has emphasized that the study of addiction genomics is an upcoming field where environment has a major role to play along with genetic predisposition. Beginning of an addiction is usually determined by the environment and the continued use of addictive substances mostly depends on genetic factors. The authors state that GWAS appears to be less conclusive in identifying genetic risk factors in alcohol dependence compared to nicotine dependence.

Various evolutionary aspects ranging from evolution of oocyte and fish immune

system to genomic landscape of primate Y chromosome are also covered. Basic process of fertilization with current concepts of integral connection of egg–sperm interactions and contribution of a combination of genomic and proteomic approaches in deciphering egg gene functions are discussed in chapter 5. The authors also suggest that the results obtained from genomic and proteomic studies are redefining the established theories and concepts of fertilization process. Adaptive immunity remains one of the major key factors that distinctly separate vertebrates from their predecessors lacking vertebrae. In chapter 6, the authors focus on evolution of a more advanced immune system in extant vertebrates like jawless and jawed fish. Serial whole-genome duplications at different stages of evolution finally leading to boney fish from the jawless ones are highly correlated with novel gene functions in vertebrate immune system. Epistasis and forward genetic screens in teleosts have already shown remarkable functional similarities between fish and mammals. Comparative genome analyses, therefore, can be used for developing new strategies to target the faulty immune systems. In chapter 4, the authors describe building of knowledge bases by dedicated efforts of complete Y-chromosome sequencing in terms of understanding the role of disease-causing mutations, gene rearrangements and genealogical tree to trace the sex-specificity in human migration, which has great importance in population genetics. The authors have also discussed the technical challenges to sequence the Y chromosome because of its highly repetitive nature. This review also covers the functional and evolutionary significance of the euchromatic regions in male-specific Y (MSY) regions and the role of isodicentric palindromes in MSY leading to gonadal dysgenesis.

Two chapters in this book are exclusively focused on derivatives of high-throughput next-generation sequencing technology. Chapter 7 is an excellent discussion on the human microbiome, starting from workflow schematics, microbial diversity and distribution in common habitats in humans to identify future thrust areas and challenges. Such metagenomic studies in humans have major influence in understanding metabolism and modulation of drug interaction in a functional milieu. The authors truly envision the usefulness of integrating metagenomic 'signature' along with genomics to decipher complexities underlying diseases. The statement about microbiome as 'our second genome' is therefore fully justified. Chapter 13 deals with an important topic of non-invasive prenatal diagnosis in the form of analysing foetal nucleic acid from maternal blood which is immensely facilitated by massively parallel sequencing methods, especially in cases of prenatal diagnosis of trisomies 21, 18 and 13. Emerging molecular counting technologies like digital PCR have become extremely handy in cases of prenatal diagnosis of monogenic disease by measuring precise allelic ratio of wild-type versus mutant alleles. The schematic illustrations throughout the article are immensely helpful for the readers to clearly understand the concepts. In chapter 12, the author has chronicled the genetic studies conducted on a common birth defect, orofacial cleft (OFC). OFC is one of the few diseases that was thought to have an inherited component even before Mendel's birth. Genome-wide linkage and association studies have resulted in huge successes in identifying causal genomic regions for OFC. The major OFC causal gene *IRF6* has been estimated to account for at least 55% cases worldwide.

The last six chapters in this book have dealt with various topics on population sampling, identification and ethical issues. Chapter 16 focuses on evolution-oriented biology education, where the author has opined that the theories of evolution should be taught in the first-year degree programme, so that the students can use these concepts in other areas of biology in their successive years. This article reminded me of the famous quote by the eminent evolutionary biologist Theodosius Dobzhansky that 'Nothing in biology makes sense except in the light of evolution'. Also, evolution-based courses should be made more interactive for easy conceptualization of difficult theories. Chapter 15 deals with identification of population using genetic data, where the authors have reviewed a number of algorithm-based methods that consider both polymorphism and linkage to group individuals into distinct populations. Ethical, legal and social issues with sample collection methodologies are described in chapter 18. The authors have suggested that the samples and data should be grouped according to different study designs such as longitudinal, disease-specific or biobanking residual tissue samples and have cautioned against a universal approach to examine issues related to consent, confidentiality and oversight as each biobank might have specific issues. In chapter 17, the authors have raised concerns over ethical issues with neonate screening using whole genome sequencing approaches while in chapter 20, the authors discuss policies and perspectives related to genetic discrimination, which is essentially defined as differential treatment modalities for asymptomatic individuals or relatives based on their real or assumed genetic characteristics. Several such reports from Canada, the USA and Australia are listed in this review and the authors have tried to assess the social and behavioural impacts of such discriminations so that proper policies can eventually be implemented. Finally, chapter 19 is focused on a tussle between sharing genomic data and privacy protection issues. Use of NGS (next-generation sequencing technologies such as massively parallel or non-optical high-throughput sequencing) is leading to enormous data generation worldwide. The time has come to develop new governance complementary to the existing one to ensure effective data sharing with compliance to ethics and legality in terms of retaining public trust on genomics research.

Overall, this volume provides an excellent educative resource for researchers in the field of genomics and human genetics. Most articles end with point-by-point summaries and future perspectives. Although the volume lacks proper thematic organization of the articles and an editorial statement, it is worth mentioning that almost all articles in this volume have informative illustrations with tables and flow-charts for lucid understanding of the subject.

ACKNOWLEDGEMENTS. I thank Partha P. Majumder, Kunal Ray and Sandeep Singh for their useful comments.

MOULINATH ACHARYA

National Institute of Biomedical Genomics,
Kalyani 741 251, India
e-mail: moulinath@gmail.com