BOOK REVIEWS

Research and applied medical genetics: filling the gap

Translating research into clinics

'Translational Research in Genetics and Genomics' by Moyra Smith

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The scientific revolution of the 19th century is without any doubt the genome sequencing, made possible by the explosive development of novel molecular technologies.

The huge amount of information on the human genome we do have now needs to be finalised for clinical purposes in the 'EU' concept of 'improving the quality of life of patients and their families'.

Therefore, I have read with great interest the book 'Translational Research in Genetics and Genomics'.

The book offers in Chapter 1 a comprehensive scenario about the current knowledge on genetic disorders. The more relevant approaches adopted and the goals achieved by isolating disease genes are described, offering a brief though exhaustive vision of the state-of-the-art. The different strategies in gene disease isolation are well described, including linkage analysis, loci mapping, DNA nucleotide (SNPs) and structural (CNVs) polymorphisms' importance and genome-wide sequencing. The author also describes some translational aspects related to polygenic common diseases, with emphasis on genetic risk evaluation.

Chapter 2 is devoted to the description of the novel significance of the genome structural variations and genomic imbalances. The overview is very clear, introducing not only the intriguing concept of the possible role(s) the surprisingly high number of CNVs in the human genome may have in genetic disorders, but also highlighting the complexity of CNV's interpretation in terms of their functional effects. In fact, although the examples cited by the author (cytogenetic magnification, mental retardation, autism, complex syndromes) are truly relevant, their translational impact in applied medical genetics is still limited to molecular cytogenetics. In the

other cases, an unambiguous causative association between CNVs and disease is still lacking and the majority of CNVs identified in complex disorders might be considered susceptible genomic regions. It is clear that only the building up of a human CNV catalogue will enable us to discriminate polymorphic regions from pathogenic variations, thereby concentrating the effort on genome imbalances with established roles in disease aetiology and pathogenesis. The author decided to review cytogenetic and complex genetic disorders only. In addition, the use of oligo-arrays (as CGH exon arrays) is not mentioned. However, this approach has been proven to be extremely useful in terms of rearrangements identification in Mendelian disorders. The sequencing approach, derived from the human genome project, has allowed a massive identification of small mutations, but it completely missed the identification of gene rearrangement; consequently, other techniques (such as the 'old-fashioned' but still cardinal Southern blot) were somehow dismissed.

The CNVs detection based on hybridisation resuscitates the identification of large rearrangements in genes, disclosing in many examples the role of this type of mutation in Mendelian diseases. Therefore, the translational meaning of CGH and CNVs in these diseases would have deserved to be cited.

In Chapter 3 the author faces the hard task of reviewing the significance of DNA-sequencing changes in diagnosis or therapy. This chapter would deserve a specific book apart; nevertheless, the author succeeds in describing most of the possible examples, though without deepening some very relevant results (as the 'conflicting' meaning of mis-sense mutations in dominant disorders,

or the translational application of antisense oligoribonucleotides splicing modulation in dystrophinopathies). However, this is understandable considering this vast field.

Chapter 4 focuses on epigenetics. The chapter aims at simply describing this phenomenon, its basis and its regulation, and cites a few examples of imprinting disorders eligible to be approached by imprinting modulation. The field is still far from the advancements already achieved in diseases based on other mechanisms; however, I would have cited the Rett syndrome, one of the more investigated neurodevelopmental disorders, because of the pathogenic effect of a methyl-binding protein defect, in which understanding the imprinting regulation will probably be the key for finding a possible therapy.

Chapter 5 introduces old and recent knowledge about late-onset neurodegenerative disorders, including Mendelian (amyotrophic lateral sclerosis and the SOD1 mutations and Huntington's chorea) and polygenic (diabetes, Parkinson's disease, dementia). Although complex, the chapter is very well structured. It focuses not only on the description of the single disease aetiology and pathogenesis, but also on general mechanisms such as oxidative stress and DNA damage, the well-described part on the role of mitochondria in late-onset diseases and consequently ageing. In addition, the very interesting topic of autophagy as the mechanism implicated in neurodegenerative disease pathogenesis is described. In particular, the chaperon-mediated autophagy is an extremely intriguing but still unravelled machinery probably having an important role in these disorders. The author also describes the proteasome pathway and the role of ubiquitination in protein degradation. The two examples of Parkinson's and Alzheimer's diseases are reported in detail with the final part describing novelties in the treatment of these disorders as lipid plasma levels as a susceptibility factor to dementia, neurotoxic chemicals, and some preliminary data on beneficial treatments with statin, anti-inflammatory drugs and antioxidants.

Chapter 6 reports on advances in treatment of Mendelian diseases. Again, the effort of the author is remarkable, but undoubtedly the field is enormous, considering the multitude of gene therapy approaches, the novel molecular therapy approaches (post-transcriptional gene silencing and antisense modulation) and the high-throughput drug discovery for modulating gene expression. Despite that, the author succeeds in describing almost all the approaches. She classified the

therapeutic strategies in small molecules treatment, substrate-reduction therapy, enzyme replacement, modifiers and epigenetic factors, and RNA-mediated molecular therapy approaches.

Understandably, the part dealing with 'classical' gene therapy is very briefly described, with some examples as haemophilia.

Chapters 7–9 report on the best-described arguments in the book. These are those related to cancer or cancer-related genetic disorders and possible treatments. It emerges clearly that the major achievements in translational research have been those reached in this field. Mendelian cancer-related disorders such as tuberous sclerosis, neurofibromatosis and Peutz–Jeghers syndrome are described with novel therapeutics already translated in clinical trials. DNA-repair diseases and toxicogenomics are also reported. Finally, the therapies on cancer disorders are updated and clearly described, very well showing the

translational application of basic research data. The author also overviews novel techniques, such as expression profiling in cancer for disease diagnosis and prognosis, and proposes 'guidelines' for cancer prognosis and therapy.

Chapter 10 recapitulates the novelties in pharmacogenetics and pharmacogenomics. These two fields of investigations will probably represent the mainstay of medical genetics in the near future, considering the possible impact they may have in predicting frequent diseases' susceptibility, drugs response, drug design, preventing side effects in therapies, and at the end, designing 'ad hoc' therapeutics. This brings us towards the concept of personalised medicine. This is a concept clearly emerging not only for genetic diseases but also for other frequent disorders, for which genetic factors may influence the disease course and the therapy efficacy. This consideration drives us to the

last Chapter, summarising the phenomic world interfacing with genetics and genomics. To this belong all the approaches aiming at organising OMIC databases (phenomic, genomic, proteomic), biobanks and genetic services.

The interaction between all these disciplines and sciences will fill the gap, allowing us to improve the translation of genetic sciences into medical genetics.

This is a very comprehensive and up-to-date book, recommendable both for young medical geneticists, but in particular to other physicians, such as neurologists, cardiologists, paediatricians and to all specialists working close to genetic disorders ■

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'Me, Myself, and Why. Understanding your own genome and evolutionary history'

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Understanding human genome complexity

'Handbook of Human Molecular Evolution' Edited by David N Cooper, Hildegard Kehrer-Sawatzki
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Peter de Knijff

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At a time when reading through your own complete genome will be technically feasible soon, it also becomes important to have access to information that will help understand your own genome complexity and genetic history in more general terms. Acquiring a fast understanding of the many essential aspects of human molecular evolution was nearly impossible because a lot of information was scattered over many different sources. With the Handbook of Human Molecular Evolution in hand (literally a challenge in itself, unless you are a professional weightlifter), you have all the information for grabs.

The handbook comes in two volumes with, combined, 1717 pages. It has a total weight of 4866 g, is the product of 377 contributors, and is edited by Cooper and Kehrer-Sawatzki.¹ Its format is somewhat different from that of many other handbooks. There are 12 different sections: Vol 1 with General Concepts in Evolutionary Genetics; Mutation, Adaptation and Natural Selection; Evolutionary and Population Genetics; Human Evolution; and Human Genome Evolution; Vol 2 with Evolution of Human Gene Structure and Function; Evolution of Gene Expression; Mitochondrial Genome Evolution; Chromosomal Evolution; Comparative

Genomics; Evolution and Disease Susceptibility; and Analysis of Ancient DNA. These sections contain 282 articles with levels of scientific complexity varying from Introductory, Advanced to Keynote. This makes this handbook accessible for different groups of readers, and reflects the editor's main ambition of covering the complete range of human molecular evolution studies for every scholar, from undergraduate to the experienced professional.

This handbook is a real treasure trove, because there are new facts and figures literally everywhere for everyone. For the experienced geneticist, the articles describing human evolution from a paleo-anthropological perspective are very helpful. For the archeologist, the articles introducing the structural complexity of genomes and population genetic statistics are very illuminating. Most sections have a very logical structure; other sections seem to contain haphazardly chosen articles. In this respect, one could wonder why in the section Human Evolution (Vol 1, pp 345–563) there are articles describing the genetic diversity of the German population and the British population, but not, for example, the Dutch, French or Greek. This seemingly lack of structure of this handbook, however, works very well for the reason that it introduces some repetition of facts. This cannot be avoided when editors choose for so many overlapping articles instead of distinctly cohesive chapters. As an example, the