Ann. Hum. Genet. (1997), **61**, 463–467
Printed in Great Britain

Reviews

The History and Geography of Human Genes. Abridged Paperback Edition. By L. Luca Cavalli-Sforza, Paolo Menozzi and Alberto Piazza. Princeton University Press, Princeton, New Jersey, 1996. Pp. 413. £25.00. ISBN 0 691 02905 9.

When *The History and Geography of Human Genes* was first published in 1994 it was met with universal admiration, being described by one reviewer as 'a crowning achievement, a compendium of a career's work, and a sourcebook for years to come' (Weiss, 1995) and by another as the raspberry chocolate cake of human population genetics: 'rich, dense, uniformly high in quality, heterogeneous in subject matter and best enjoyed by repeatedly removing from the ... bookshelf to take small bites' (Diamond, 1994). However, this compelling volume was, in its first incarnation, over 1000 pages in length and cost £120 and was therefore a daunting purchase for all but the most dedicated anthropological geneticist. The new abridged edition (missing the tables and colour maps of global allele frequency distribution which comprised half the original volume) is considerably shorter, and at one-fifth the price, finally accessible to anyone interested in the genetic ancestry of our species.

The unmodified text, co-authored by Luca Cavalli-Sforza and his long-time Italian collaborators Menozzi and Piazza, is an impressive overview of human population relationships at the genetic level, summarized and interpreted in the light of archaeology, linguistics, and biological anthropology. The sheer breadth of coverage is staggering, with a global consideration of gene frequency distributions being followed by chapters devoted separately to Africa, Asia, Europe, the Americas, and Oceania (largely Australia and New Guinea). The downside of such encyclopaedic coverage, of course, is some lack of depth. No doubt archaeologists and linguists familiar with specific geographic regions will find relevant descriptions oversimplified or superseded by more recent research. The presentation of the genetics is similarly limited, both by its reliance on a data set made up of only 'classical' genetic markers (i.e. blood group, protein, and enzyme variants) rather than newer DNA polymorphisms, and, to a lesser extent, in the choice of methods used to analyse those data. Still, as long as *The History and Geography of Human Genes* is recognized for what it is, a research monograph, and not mistaken for a comprehensive review of current research in the field of human population genetics, these shortcomings pale in the light of the ensuing synthesis.

The authors analysed the world-wide distribution of human genetic variation using allele frequencies for 120 loci and 491 populations, comprising data collected from the literature published until 1986. Two main methods were used to summarise this enormous collection of data: phylogenetic trees (sometimes called dendograms) of population relationship constructed from matrices of pairwise genetic distances between populations, and 'synthetic maps' describing the geographic distribution of principal-components of populations' genetic variation. These synthetic maps are an analytical speciality of Paolo Menozzi and differ from more traditional allele frequency maps in depicting the spatial distribution of gene frequency differences at multiple loci simultaneously. In this way, overall patterns of genetic relationship may be identified which are likely to correspond to the effects of population movements (migration and associated gene flow) among particular regions. For the authors, trees provide an 'expression of history', a representation of the likely temporal sequence of population fissions at the root of human genetic differentiation, whereas synthetic maps reflect the influence of geography, demonstrating in particular the contribution of geographic distance to genetic isolation.

The difficulty with this methodological dichotomy is that the same data are used for both types of analyses and the assumptions implicit to building trees from gene frequency data, namely that populations are closed units which diverged in a series of discrete fissions and have since been evolving independently at a constant rate, can be rejected by the clear evidence for the influence of interpopulation gene flow present in the principal-component maps. Thus, with events underlying gene frequency distributions in synthetic maps undateable and the dating of

putative population fissions inferred from trees only likely to mislead, Cavalli-Sforza and colleagues describe, but never really convincingly explain, the observed genetic differentiation. This is because it is extraordinarily difficult to tell precisely which events contributed to the patterns observed. For example, it is impossible with these data to explain adequately the unusual genetic make-up of the Khoisanid San, a Southern African population with a high proportion of Asian alleles. It may be that the observed gene frequency distribution reflects recent admixture with a west Asian population. Alternatively, the San may best be regarded as a 'fossil' group, representing the nearest approximation to the ancestral human population from which all Asian and African populations subsequently derived.

It could be argued that the strength of *The History and Geography of Human Genes* lies less in its explanatory power per se and more in its ability to identify and articulate clearly the questions which remain unanswered. Fundamental to the continued elucidation of human population relationships is further sampling and the authors spend considerable time in their continent-specific discussions, and then again in the book's epilogue, highlighting those regions most deserving of attention. A major theme running through their discussion is that of the Human Genome Diversity Project, a venture proposed by Cavalli-Sforza, the late Allan Wilson, and others, which aims to collect, and immortalise in cell lines, DNA collected from populations around the globe (Cavalli-Sforza *et al*. 1991). Unfortunately, this initiative has been plagued both by bad publicity and a lack of consensus among human population geneticists regarding the best strategy for geographic sampling. In their epilogue, Cavalli-Sforza and colleagues present their criteria for effective sampling, with the focus squarely on the analysis of indigenous (unacculturated) groups whose degree of admixture with surrounding populations is either known or negligible. Whether such sampling is feasible, or even appropriate to analyses using DNA markers is unclear and will not be resolved effectively without further research. It is now up to the next generation of investigators, with this 'bible' tucked under their arms, to continue the research and move ever closer to a complete understanding of human genetic diversity.

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Does It Run in the Family? A Consumer's Guide to DNA Testing for Genetic Disorders. By DORIS TEICHLER ZALLEN. New Brunswick, NJ, London: Rutgers University Press, 1997. Pp. 201.

I had just returned from the prenatal clinic, having given the diagnosis of neural tube defect to a couple who were devastated at the news. Some of their questions were; What is spina bifida?, How do we find out more?, What does mild mean?, How do further diagnostic tests help us make decisions?, What about future pregnancies? Can we get more information somewhere?

This book is for all couples in this position, and others like them, who have just become aware of genetic problems within a family. Dr Zallen describes the book as a 'consumer's guide to DNA testing for genetic disorders'. This book gives answers to the above questions, tells the consumer why geneticists act the way they do, and how genetic testing works the way it does.

Nine chapters of wisdom, elegantly explained in not too difficult language, guide the consumer through the maze of genetic problems when met with a new diagnosis in the family. A short overview and introduction leads in to chapter 2 – the basics of genetic inheritance in one easy chapter. She mentions the genetic 'grapevine' – a series of Chinese whispers that distort and panic family members when conflicting accounts are misinterpreted and distorted, and usually out of date when relatives pass on information second hand – an experience we are all familiar with.

Chapter 3 details methods about finding out more about genetic tests – what the genetics team can and *cannot* do, and what consumers can and cannot do. There is derision about the use of the word positive in the context of genetic test results as this means the opposite of the usual meaning of good news. There are tips on getting the most out of genetic counselling. The chapter

on making decisions about genetic testing, gives useful background to direct DNA testing and linkage testing, and clearly explains linkage in the context of 'why can't you just test me? what do you mean I have to get [blood from] my aunt and mother and brother?' There is a logical explanation of the moral duty to share information with others in the family, if it is beneficial, even though there is no legal duty, and Zallen shows the counter situation of a couple who complain 'why didn't other relatives tell me?', when so often the pain being experienced could have been easily avoided.

There is a good chapter on making decisions about testing for genetic susceptibility, which is up to date with BRCA1 and Alzheimer gene testing. Chapters six and seven reflect on society's abuse of genetic tests, and the outlook for the future. Chapter eight gives advice on nuturing the genetic grapevine, and helpfully explains how several physicians are 'simply *not* experts when it comes to genetic matters'. Some consumers have noted with understatement that their physician 'wasn't particularly helpful'.

Chapter nine proffers some thoughts and recommendations. The three recommendations are: (1) Consumers need accurate genetic information at the very beginning of their awareness of a genetic problem; (2) Consumers need to have access to genetic services and to more kinds of educational tools as they make decisions about genetic tests, and (3) Better methods of keeping consumers informed over time are essential.

These could provide a suitable mission statement for all genetic centres, and the best way to achieve this would be to give all consumers a copy of the book to read before they are seen by the geneticist. It would certainly make the job easier! In practice, however, easy access to this book will help all couples. The best part of the book may be the appendix which provides a wealth of information sources for patients and a link to an updated list on the internet at

`http://www.cis.vt.edu/pages/zallen`.

To send the consumer away to their computer or local library with this address and the title of the book scribbled on a piece of paper, may be some of the best advice that they could have. Our head of department, an expert teacher, spent a long time counselling a couple recently, with a strong family history of muscular dystrophy. At the conclusion when asked if they wanted to clarify any points, the comment of 'do you mean to say that this is hereditary, Professor?', was not a reflection on the quality of the explanation, by any means, but the often standard response to being given information that is always a shock, once the ramifications start to sink in.

'Does it run in the family' is a very appropriate title – most users of this book will have answered 'yes', but will also have found that the fear and ripples following diagnosis of a genetic problem certainly do run through a family – grief and reaction is a dominant response with virtually complete penetrance. Zallen provides a little gene therapy for this nasty condition.

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DNA Sequencing Strategies: Automated and Advanced Approaches (An EMBO Practical Course). Edited by W. ANSORGE, H. VOSS and J. ZIMMERMAN. Chichester: J. Wiley & Sons, Heidelberg: Spektrum Akademischer Verlag. 1997. Pp. 202. £32.50, $50.00 (spiral-bound paperback).

This book is based on the protocols of a European Molecular Biology Organisation (EMBO) practical course which was designed to provide scientists with access to the most recent sequencing developments. The editors do not claim to be replacing the 'hands on' guidance which comes from attending such a course but wish to promote 'severely tested protocols' and the use of up-to-date methods for DNA sequencing.

The first three chapters include protocols for cloning and preparation of templates and sequencing itself. The relative merits of directed or random sequencing strategies or a combination of both are discussed to allow the reader to make an informed choice as to which will best suit individual needs. A number of alternatives are presented for each strategy. Useful sections on bacterial transformation and vector/host selection are also included. The pages devoted to the preparation of template DNA for PCR and sequencing include protocols for the preparation of M13 and plasmid DNA, and for the purification of PCR products, prior to sequencing. Details of

the DNA sequencing protocols themselves, as the title suggests, are tailored entirely for automated approaches. The relative merits of various radioactive isotopes used in manual sequencing protocols are not discussed. The protocols described can be used on any automated DNA sequencer but are primarily designed for automated DNA sequencing devices working in the 'one-dye/four lanes mode'. For the ABI DNA sequencer, usually working in a 'four-dye/one lane mode', modifications in the software have been reported that adjust the instrument to the one dye/four lanes mode but users should note that these modifications are only referenced in this book. Protocols for both T7 DNA polymerase and thermostable DNA polymerase are included with either internal or primer labelling. Sequencing from both strands of double stranded templates using two labels is described for the EMBL 2-dye DNA sequencer.

The second half of the book details synthesis and purification of primers, preparation of DNA sequencing gels, electrophoresis and computer analysis. The primer chapter provides background information about primer selection, optimization, synthesis and purification. Details of the preparation of DNA sequencing gels and electrophoresis outline the procedures used for an ALF DNA sequencer and as they are brief they are probably of limited use. The final chapter demonstrates the DNA sequence assembly process and sequence analysis using the program package GeneSkipper, which was developed at EMBL. This is only of real practical use to readers employing this package, although it does illustrate how data analysis is facilitated and accelerated by the use of specialised computer tools.

The book is well presented, the protocols being supplemented with more than 100 data charts, tables and photographs. The spiral binding lends itself well to the editors claims that this is a 'user friendly laboratory bench reference', and most chapters fall into this category, with the possible exception of the last two. All the methods appear to be up to date, detailed and easy to follow. The comments and pitfall sections are extremely useful and give the reader an improved understanding and feel for the techniques. Although this book is designed for users of automated sequencers, the three chapters on cloning, template preparation and primer design are relevant for all types of sequencing, be it automated or manual. The editors have written with clarity and have comprehensively covered the various sequencing strategies which abound.

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Mutation Detection. By Richard G. H. Cotton. Oxford: Oxford University Press. 1997. Pp. 198. £22.50 (paperback).

'Mutation detection is time-consuming and expensive and thus should be undertaken with a thorough knowledge of the many methods available', the book cover states. When one considers the number of academic and commercial activities dependent on characterization of DNA variations, in any context, there is surprisingly little core academic activity, although there are very many 'end users'. Mutation detection is a methodological domain bridging an interface between biology and technology, thus bridging also academic and commercial sectors and funding agencies. Cotton's book is an elegant and balanced account of mutation detection, setting the subject in a truly academic format. Both the historical developments and basic principles are brought together in a clear and very thorough way, and the presentation should empower the reader to 'go away and think for himself'. The book is a distinct contrast from another excellent book published by O.U.P. *Laboratory Protocols for Mutation Detection* edited by Ulf Landegren, based on a HUGO supported Mutation Detection meeting in Sweden in 1995. The latter has protocols contributed by a wide range of method inventors, including Cotton, and was published in 1996. By contrast, Cotton's preface is dated April 1995 and his book is published in 1997. While the latter book does give some abbreviated protocols, it is not its main objective. Indeed, the time between writing and publication for this sole author book in an intensely active field, means that many 1995–7 developments are not included. In that time, mass spectrometry, chip developments and various new 'low tech' methods have become significant. Nevertheless, I would recommend this book to anyone with a need to understand mutation detection rather than simply following protocols. That understanding depends much more on basic principles and significant historical landmarks, than on the latest method. The detail given is considerable, and the author has structured the chaos of developments into a comprehensive overview.

Methods concerned with repeat length variations (trinucleotides, microsatellites, VNTRs) are either deliberately omitted, or very brief. In view of their major importance in disease, linkage research and identity testing, any future edition would benefit from their inclusion. However, these omissions are compensated by an introduction which covers general background, ethics, academic/commercial relationships, nomenclature and mutation databases. These are the spokes which link mutation detection to its applications and utility. The preface points up the interest in mutation detection from response to reviews. I second that both from national and international meetings and from a recent local meeting which was unexpectedly overbooked. Had I known that Cotton's book was now published I would have cited it as a recommended reading. Remarkably, there is no other treatise dedicated to mutation detection, although there are many multi-author protocol manuals, but in 198 pages this is an outstanding little book anyway.

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Genetics of Human Neoplasia. Volume 3 of Advances in Genome Biology. Edited by RAM S. VERMA. JAI Press, London. 1995. 2 Vols: Pp. 232 & Pp. 248. £125.00 (US$195.00). ISBN: 1 55938 835 8.

Genetic analysis of cancer cells has led to the identification of numerous regulatory pathways in the cell. These discoveries are of critical importance for our understanding of the molecular basis of cancer, and they thus facilitate new approaches to prevention and treatment. Although Volume 3 of Advances in Genome Biology does not set out to provide coverage of all aspects of cancer genetics, it does contain many excellent overviews.

Tumour suppressor genes are dealt with in several chapters, including an excellent survey by Weissman and Conway which combines data from somatic cell and molecular genetic studies. It is a little frustrating that practical aspects of loss of heterozygosity (LOH) are considered in a separate chapter in a different volume! However, this interesting chapter, by Zedenius and colleagues, did contain some useful considerations for performing LOH analysis of a new set of tumours. I highly recommend the outstanding, subtantial review by Soussi on the p53 gene and protein. Several pages have been added in proof updating important discoveries on p53 in relation to cell cycle control, structural studies, apoptosis and therapy.

Himelstein and Muschel provide a comprehensive survey of the role of oncogenes in a variety of processes associated with tumour progression, such as angiogenesis, metastasis, cell adhesion, proteolysis, drug and radiation resistance. An interesting chapter by Cox examines the role of transcription factors in cancer. Rothberg and Heruth have also written an excellent chapter on non-fungal '*myc*-Ology', which contains an extensive survey of fundamental aspects of normal and aberrant c-*myc*. Areas which are not covered are included in the substantial reference list. The role of the ras oncogene in signal transduction is reviewed briefly but with a good reference list by Bos and Burgering.

It is a pity that this volume was published approximately two years (Sept 1995) after the chapters appear to have been written. Nevertheless, it provides an interesting and useful framework for anyone interested in cancer genetics.

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