

## Genes and Common Diseases

*Genes and common diseases* presents an up-to-date view of the role of genetics in modern medicine, reflecting the strengths and limitations of a genetic perspective.

The current shift in emphasis from the study of rare single gene disorders to common diseases brings genetics into every aspect of modern medicine, from infectious diseases to therapeutics. However, it is unclear whether this increasingly genetic focus will prove useful in the face of major environmental influences in many common diseases.

The book takes a hard and self-critical look at what can and cannot be achieved using a genetic approach and what is known about genetic and environmental mechanisms in a variety of common diseases. It seeks to clarify the goals of human genetic research by providing state-of-the-art insights into known molecular mechanisms underlying common disease processes while at the same time providing a realistic overview of the expected genetic and psychological complexity.

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Cambridge University Press  
978-0-521-54100-8 - Genes and Common Diseases  
Alan Wright and Nicholas Hastie  
Frontmatter  
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**Alan Wright**

**Nicholas Hastie**

***Foreword by David J. Weatherall***



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CAMBRIDGE UNIVERSITY PRESS

Cambridge, New York, Melbourne, Madrid, Cape Town, Singapore, São Paulo

Cambridge University Press

The Edinburgh Building, Cambridge CB2 2RU, UK

Published in the United States of America by Cambridge University Press, New York

[www.cambridge.org](http://www.cambridge.org)

Information on in this title: [www.cambridge.org/9780521833394](http://www.cambridge.org/9780521833394)

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First published 2007

Printed in the United Kingdom at the University Press, Cambridge

*A catalog record for this publication is available from the British Library*

*Library of Congress Cataloging in Publication data*

Wright, Alan F., MRC.

Genes and common diseases / Alan Wright and Nicholas Hastie.

p. ; cm.

Includes bibliographical references and index.

ISBN-13: 978-0-521-83339-4 (hardback)

ISBN-10: 0-521-83339-6 (hardback)

ISBN-13: 978-0-521-54100-8 (pbk.)

ISBN-10: 0-521-54100-X (pbk.)

1. Medical genetics. I. Hastie, Nicholas. II. Title.

[DNLM: 1. Genetic Predisposition to Disease. QZ 50 W947g 2007]

RB155.W75 2007

616'.042-dc22

2006102406

ISBN-13 978-0-521-83339-4 hardback

ISBN-10 0-521-83339-6 hardback

ISBN-13 978-0-521-54100-8 paperback

ISBN-10 0-521-54100-X paperback

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## Foreword

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The announcement of the partial completion of the Human Genome Project was accompanied by expansive claims about the impact that this remarkable achievement will have on medical practice in the near future. The media and even some of the scientific community suggested that, within the next 20 years, many of our major killers, at least those of the rich countries, will disappear. What remains of day-to-day clinical practice will be individualized, based on a knowledge of a patient's particular genetic make-up, and survival beyond 100 years will be commonplace. Indeed, the hyperbole continues unabated; as I write a British newspaper announces that, based on the results of manipulating genes in small animals, future generations of humans can look forward to lifespans of 200 years.

This news comes as something of a surprise to the majority of practicing doctors. The older generation had been brought up on the belief that most diseases are environmental in origin and that those that are not, vascular disease and cancer for example, can be lumped together as “degenerative”, that is the natural consequence of increasing age. More recent generations, who know something about the interactions between the environment and vascular pathology and are aware that cancer is the result of the acquisition of mutations of oncogenes, still believe that environmental risk factors are the major cause of illness; if we run six miles before breakfast, do not smoke, imbibe only homeopathic doses of alcohol, and survive on the same diets as our

hunter-gatherer forebears, we will grow old gracefully and live to a ripe old age. Against this background it is not surprising that today's doctors were astonished to hear that a knowledge of our genetic make-up will transform their practice almost overnight.

The rather exaggerated claims for the benefits of genomics for clinical practice stem from the notion that, since twin studies have shown that there is a variable genetic component to most common diseases, the definition of the different susceptibility genes involved will provide a great deal of information about their pathogenesis and, at the same time, offer the pharmaceutical industry many new targets for their management. An even more exciting prospect is that it may become possible to identify members of the community whose genetic make-up renders them more or less prone to noxious environmental agents, hence allowing public health measures to be focused on subgroups of populations. And if this is not enough, it is also claimed that a knowledge of the relationship between drug metabolism and genetic diversity will revolutionize clinical practice; information about every patient's genome will be available to their family practitioners, who will then be able to adjust the dosage of their drugs in line with their genetic constitution.

Enough was known long before the completion of the Genome Project to suggest that the timescale of this rosy view of genomics and health is based more on hope than reality. For example, it was already clear that the remarkable phenotypic diversity of single gene disorders, that is those whose inheritance follows a straightforward Mendelian pattern, is based on layer upon layer of complexity, reflecting multiple modifier genes and complex interactions with the environment. Even after the fruits of the Genome Project became available, and although there were a few successes, genome-wide searches for the genes involved in modifying an individual's susceptibility to common diseases often gave ambiguous results. Similarly, early hopes that sequence data obtained from pathogen genomes, or those of their vectors,

would provide targets for drug or vaccine development have been slow to come to fruition. And while there have been a few therapeutic successes in the cancer field – the development of an agent directed at the abnormal product of an oncogene in a common form of human leukemia for example – an increasing understanding of the complexity of neoplastic transformation at the molecular level has emphasized the problems of reversing this process.

In retrospect, none of these apparent setbacks should have surprised us. After all, it seems likely that most common diseases, except monogenic disorders, reflect a complex interplay between multiple and variable environmental factors and the individual responses of patients which are fine-tuned by the action of many different genes, at least some of which may have very small phenotypic effects. Furthermore, many of the refractory illnesses, particularly those of the rich countries, occur in middle or old age and hence the ill-understood biology of aging adds yet another level of complexity to their pathogenesis. Looked at in this way, it was always unlikely that there would be any quick answers to the control of our current killers.

Because the era of molecular medicine is already perceived as a time of unfulfilled promises, in no small part because of the hype with which it was heralded, the field is being viewed with a certain amount of scepticism by both the medical world and the community at large. Hence, this book, which takes a hard-headed look at the potential of the role of genetics for the future of medical practice, arrives at a particularly opportune time. The editors have amassed an excellent team of authors, all of whom are leaders in their particular fields and, even more importantly, have worked in them long enough to be able to place their potential medical roles into genuine perspective. Furthermore, by presenting their research in the kind of language which will make their findings available to practising doctors, they have performed an invaluable service by interpreting the complexities of genomic medicine for their clinical colleagues.

The truth is that we are just at the beginning of the exploration of disease at the molecular level and no-one knows where it will lead us in our search for better ways of controlling and treating common illness, either in the developing or developed countries. In effect, the position is very similar to that during the first dawns of microbiology in the second half of the nineteenth century. In March 1882, Robert Koch announced the discovery of the organism that causes tuberculosis. This news caused enormous excitement throughout the world; an editorial writer of the London *Times* newspaper assured his readers that this discovery would lead immediately to the treatment of tuberculosis, yet 62 frustrating years were to elapse before Selman Waksman's announcement of the development of streptomycin. There is often a long period between major discoveries in the research laboratory and their application in the clinic; genomics is unlikely to be an exception.

Those who read this excellent book, and I hope that there will be many, should be left in no doubt that the genetic approach to medical

research and practice offers us the genuine possibility of understanding the mechanisms that underlie many of the common diseases of the richer countries, and, at the same time, provides a completely new approach to attacking the major infectious diseases which are decimating many of the populations of the developing countries. Since we have no way of knowing the extent to which the application of our limited knowledge of the environmental causes of these diseases to their control will be successful, it is vital that we make full use of what genomics has on offer.

We are only witnessing the uncertain beginnings of what is sure to be an extremely exciting phase in the development of the medical sciences; scientists should constantly remind themselves and the general public that this is the case, an approach which is extremely well exemplified by the work of the editors and authors of this fine book. I wish them and their publisher every success in this new venture.

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