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Book Review

Genotype to Phenotype, 2nd edition, edited by S. Malcolm and J. Goodship, Bios Scientific, Oxford 2001.

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It is particularly important in our information age to stay tuned to major scientific advances through reports or papers which are not only valid and indicative of the latest discoveries, but, in addition, can be informative in relation to the major directions of contemporary and future research. This is accomplished beyond any doubt in the reviewed collection of papers. Malcolm and Goodship have included in the second edition of their book (after the successful career of the first edition) examples of a more applied research into molecular genetics; their aim and hope is to further elucidate both the problem of the definition of a gene (whether by genotype or phenotype) and the complex relation (which develops through various environmental or genetic stimuli) between the phenotype and the genotype.

A more detailed look into the specific papers contained in the second edition will clarify how the editors attempt to achieve their aims. The papers can be divided into two broad categories: a) the more theoretical (which are more attractive to the biology-genetics informed general public), and b) the more technical (which will undoubtedly benefit the genetics specialists). Examples of the more technical and applied are the papers: Wazel, Lipoldova and Demant's "Identification of disease susceptibility genes (modifiers): cancer and infectious diseases"; D. T. Bonthron's "The GNAS1 gene"; Christian and Ledbetter's "Genomic disorders"; Worth and Wood's "Genotype to Phenotype in the spinocerebellar ataxias"; D. R. Fitzpatrick's "Disorders of cholesterol biosynthesis"; F. R. Goodman's "Mutations in the human HOX genes"; Murray and Semina's "PITX2 gene in development"; Allen E. Bale's "The hedgehog pathway and developmental disorders"; Gaspar and Kinnon's "X-linked immunodeficiencies"; and Price and Mitch's "The ubiquitin-proteasome system and genetic diseases: Protein degradation gone awry". The more theoretical include Sue Malcolm's "Genotype to Phenotype: interpretations of the human genome project"; Sylvia B. Nagl's "From protein sequence to structure and function"; François Cambien's "Genes in population"; Humphries, Talmud and Montgomery's "Gene-environment interaction: lipoprotein lipase and smoking and risk of CAD and the ACE and exercise-induced left ventricular hypertrophy as examples"; Ann K. Daly's "Pharmacogenomics"; and Chinnery and Turnbull's "Mitochon-

drial genetics". Here, I will refer in more detail to the more theoretical, leaving the more technical only with the above remark that they are definitely examples of research, which should not be missed by the molecular genetics specialists.

In the Preface, Malcolm and Goodship lay out the unity of approach in the papers contained in the collection: they either use web based tools (such as BLAST) and experimental techniques (such as yeast two hybrids and microarray assays, which are outlined in more detail in Nagl's article) to determine the structural relation of one gene with another in the genetic sequence, or they investigate the relation between genotype and phenotype through the study of mutations of genes and their role in the disorder phenotype. They also investigate the relation of environmental factors such as smoking, illnesses and pharmacological agents to the phenotypic polymorphic manifestation of a gene or its mutation.

Whatever the editors' view about the unity of approach in the papers contained in the collection may be (which also explains the title of the book: *Genotype to Phenotype* –and not *Phenotype to Genotype*), the careful reader will notice that their majority try to determine the way the genes interact or a gene's structural function by its or its mutation phenotypic manifestation, rather than the other way around. This obviously limits the predictive power of the conclusions of the papers in question. Perhaps here there may be a difficulty in the resourcefulness and application of the predictive tools of the trade at this point of time (something the editors also admit in the Preface), and perhaps in the not so distant future this difficulty will be overcome; the issue still remains however, that unless the predictive force of the conclusions of the mentioned papers is not strengthened, the overall scientific value of the related research will remain in doubt. This mentioned the fact still remains that the collection contains, at least in seminal form, many of the scientific discoveries of the 21st century in molecular genetics.

A brief reference to the main conclusions of the papers may help the potential reader to realize this. Malcolm's paper, which provides a quite interesting historical account of the discoveries associated to the genome project, indicates in its conclusion the main worries of the scientific community of geneticists for the next 5-10 years: Malcolm claims that the publication of the entire human genome is only the beginning of a journey, rather than the end. There is need of a tremendous amount of research in the way the splicing mechanisms work, as well as in the function and operation of the regulatory regions in the genome. This research can only produce results with adequate predictive power through the careful experimental study of the significance of sequence variants. Till this research has advanced to a great extent we cannot have the full benefits of the remarkable work carried out by the geneticists involved in the human genome project.

Nagl's much more optimistic paper analyses in detail the way recent technological and methodological advances in computer science can lead the newly emerged and interdisciplinary field of Bioinformatics into a more integrated role in the genetics discovery process. She investigates the example of the advances in oncogenetics and illustrates how newly developed experimental and computational methods can be linked to a biological model so that theoretical predictions (for example, theoretical predictions in oncogenetics based on the study of genetic sequence variation and the polygenic nature of proteins) can be directly tested in the laboratory, and the results can be fed back for creating refinements in the theoretical model. She offers diagrams, figures and tables to illustrate this example and concludes that we will shortly arrive to a new and more complex conception of protein function; this more adequate comprehension of protein function (which will include the parallel-processing properties of tissue or organism-wide interaction networks) will be brought about by the sequence, structure, interaction

and network analysis provided by bioinformatics and computer science newly applied analysis algorithms.

Cambien's quite insightful contribution enlightens yet another application of the theory related to phenotype manifestations of a particular genotype: the quite interesting and quite theoretical (as yet) fields of evolutionary genetics, population genetics and genetic epidemiology. In these fields there are particular problems in methodology which one needs to overcome before he/she can achieve an adequate predictive power in his/her conclusions: for example, in human population genetics males and females assemble in a random (and not easily calculable) way to produce offspring. Here the Hardy-Weinberg principle may help greatly in establishing statistically significant correlations, but leaves much to be desired in determining an adequate explanation of the way mutation and recombination of genes help to formulate a specific demographic history in a given population. Cambien proceeds into investigating evolution and natural selection in human populations based in the formation and exchange of amino acids and infectious diseases (such as hemoglobinopathies, malaria and HIV-1), as well as skin pigmentation, cardiovascular diseases, vitamin C consumption related genes and obesity. At this point Cambien also discusses briefly the argument of Gould and Lewontin (1979) that "the immediate utility of an organic structure often says nothing at all about the reasons of its being"; its treatment however, is highly objectionable (no critical discussion or at least explanation of why this argument does not have any deleterious consequences for Cambien's main points) and does not give any merit to the otherwise quite interesting paper. Other points that Cambien discusses are random genetic drift, the age of polymorphisms and the human phylogeny, and the role of linkage disequilibrium and haplotypes in the genotype-phenotype association studies. Cambien concludes that not only the study of environmental stimuli, but, in addition, the study of haplotypes and alleles, strong selection and genetic drift can lead us to a better understanding of human evolution. This understanding according to Cambien can not be fully achieved, unless geneticists produce a catalog containing all common forms of human genes.

Humphries, Talmud and Montgomery's work is extremely interesting particularly for all those who need extra scientific help in combating intoxicating and dangerous to health (but widely available) substances such as tobacco. It is important to note however, that the researchers' primary task is a different one: to bypass the difficulty of studying directly the disease-causing mutations in order to identify those at risk (by a simple DNA test), they try to determine the environmental factors which lead to dangerous mutations via the identification and study of the general population sub-groups with a specific and potentially dangerous to health behavioural pattern. In particular their effort focuses on determining whether the conferred risk of a given (and potentially dangerous) mutation is very much higher is specific population subgroups. They made a very careful study of the common problems in the physiological systems' attempt to maintain homeostasis and their subsequent failure when Coronary Heart Disease is near, and the researchers cite in their paper in detail the studies that associate these problems with CAD "intermediate phenotypes", the later being directly responsible for elevated plasma level of lipids, fibrinogen, homocysteine and lipoprotein-cholesterol abnormal levels. Another factor, which was carefully studied, was also the operation of the inflammatory system as the key cause of the atherosclerotic process. Having in mind that specific environmental challenges such as smoking and alcohol consumption, as well as obesity, diabetes and increasing age are potentially clinically relevant for gene-environment interactions (which can make more dangerous the CAD intermediate phenotypes), the researchers found that smoking is particularly important in such gene-

environment interaction and took upon themselves to establish exactly how important this factor is. Through a detailed investigation in the associated genes' behavior after an environmental challenge such as smoking the researchers found that that smoking is the key environmental stress which amplifies the problematic genotype effect in the general population (three unrelated population subgroups were studied). They also found that removing this environmental challenge (smoking) diminishes this effect. Using their research as a basis, the researchers concluded that in the next few years it may be possible to advise effectively patients not to engage in specific environmental challenges which will cause CAD, based on their genetic information. It may be also possible, according to the researchers, to cure the patients who already exhibit the disease via blocking the LPL bridging functions and via the use of novel drugs such as ACE inhibitors at the molecular level.

Even though, this prediction may be a definite next day in the genetically applied therapeutic methods for CAD, the detailed study of Humphries et al is definitely a much needed weapon in the currently not so successful anti-smoking campaign of WHO, UN and EU health agencies and organizations.

Ann K. Daly's contribution investigates the fascinating field of pharmacogenomics or the study of the genetic factors that determine drug efficacy and toxicity and is closely allied to the subject of pharmacogenetics or the study of the genetics of drug metabolism and other genetic factors of drug efficiency such as receptors. According to Daly's research it is possible (and very soon imperative) to study DNA sequence so that the consequences of inter-individual variation in sequences of genes encoding drug targets and drug metabolizing enzymes can be analysed and taken into careful consideration when designing and developing new drugs, and when we try to individualize drug therapy with existing drugs. Daly's research moves in this direction through a careful investigation of many families of genes, such as the cytochrome P450s polymorphisms and the interesting ethnic variations that this supergene family exhibits, the N-acetyltransferase 2 polymorphism, thiopurine S-methyltransferase polymorphism and other polymorphisms which affect both drug metabolism and disposition, as well as drug response and drug toxicity. Daly concludes that in the not so distant future genotyping will help physicians to determine which drug will benefit the patient best and what dose should be used in many diseases, with the diabetes mellitus, asthma and hypertension being probably the first.

This development however, raises important ethical problems, which Daly herself (referring to the important paper of Issa, 2000) acknowledges. The prospect of investing a lot of resources for new drug design and development which are good only for Caucasians may mean a respective decrease in the attempts to design new drugs for the rest of the humankind. Taking account the globalized nature of our societies this means that in the cases of epidemics we will have drugs which will be efficient only for one race rather than another. This overtly - and easily exploitable- racist genetic prospect of the quite recent genetic research developments outlined by Daly's paper is something that international health organizations and agencies (such as the WHO, and UN and EU related agencies and organizations) need to examine in detail, before it is too late, especially after much contemporary concern for the many stocked and under development biological and chemical weapons.

Finally, P. F. Chinnery's and D. M. Turnbull's contribution concerns recent developments in the genetics of mitochondria or the ubiquitous intracellular organelles that are essential for aerobic metabolism. Even though mitochondrial genetics is relevant to many rare and not so rare nuclear genetic disorders (such as Friedreich's ataxia, Wilson's disease, and autosomal recessive hereditary spastic paraplegia), Chinnery's and Turnbull's contribution

deals mainly with the direct consequences of the defects of the mitochondrial genome. They investigate the biochemistry related to the unusually high mutation rate of mtDNA, and, in more detail, the pathogenic mtDNA defects, which are caused by rearrangements, deletions and point mutations. They find that one of the most serious difficulties of their task is to explain the striking difference in phenotype seen amongst different patients with an identical genetic defect. They try to deal with this difficulty by the separate study of cases having variations in the level of heteroplasmy and tissue-specific thresholds and differences in phenotype due to nuclear and environmental factors. They conclude that this part of their study has to remain at this time with some questions unanswered (for example in relation to differences in the time that the problematic phenotype occurs or the possibility of a relapse or remittance). They finish their study with three quite important sections: the study of hereditary pathogenic mtDNA defects, how to deal with patients with suspected mtDNA disease, and the therapeutic manipulation of the mitochondrial genome (through concentric exercise training programs, inhibition of the replication of mutant mtDNA or even delivering a self-replicating plasmid into mitochondria).

Having carefully studied the quite informative collection of articles in molecular genetics and in particular the relation of genotype to phenotype, one is left with a feeling that is both bitter and sweet: sweet, because he/she is confident that the quite remarkable wonders which the book predicts will not take long to be materialized (once the methodological and many practical and material difficulties are met effectively); bitter, because of the many dangers that these discoveries may bring to the human race, if allowed in the wrong hands, or associated to the wrong pursuits and purposes. Unfortunately, the prospects of international corporations using this quite frontier research into genetics for private or corporate gains, instead for the salvation of life on earth and its qualitative improvement, as well as the racist appropriation of pharmacogenomics, are dangers that having in mind the recent and not so beneficial history with similar discoveries in physics can do nothing more but alarm the general public. I sincerely hope that geneticists prove wiser than the physicists in how to appropriate and assimilate their hard-earned work.

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