

Keeping Genetics Simple

'That which is simple is wrong

That which is complicated is useless.'

Paul Valery, quoted in The Origins of Cancer, (1)

Following the rediscovery of Mendel's work, the onset of the 20 century witnessed an initial conflict and subsequent resolution of the conflict, between those who thought of inheritance as comprising discrete traits, as with Mendel's peas, and those who thought of inheritance as primarily comprising Gaussian traits, or what we would now call genetically complex traits (2). With hindsight it seems difficult to understand the difficulty over the synthesis of these two ideas, put most simply as the familiar observation that as it gets larger the binomial distribution approximates to a normal or Gaussian one.

As we enter the 21st century we see an echo of this earlier debate looming large again. On the one hand we have got used to the technical prowess of modern genetics 'solving' disorders that show a clear pattern of inheritance, such as epidermolysis bullosa or Darier's disease, or even quasi-Mendelian traits such as red hair (3–6). On the other hand the diseases we see most commonly in the clinic, psoriasis, atopic dermatitis and acne show a complex and therefore non-Mendelian pattern of inheritance. Will the technical prowess of modern genetics 'solve' these disorders to make once more a seamless transition between Mendelian genetics and complex disorders? Or will the current hyperbole by many—not least the pharmaceutical industry—prove unfounded.

Several papers published outwith the dermatological literature over the last year are germane to this issue (7–10). In this mini-review we attempt to extrapolate from this work for an audience interested in the common skin diseases. To add perspective to our argument we first start with an outline of the strengths and achievements of the molecular genetics of Mendelian disorders.

Mendelian genetics

For the majority of the last century, with the exception of the description of the mode of inheritance of a disease and consequently the facility to predict inheritance in some disease kindreds, genetics had little relevance to everyday clinical practice or even most clinical science. Experimental genetics was confined to the study of simple model organisms that could be crossed experimentally and maps of loci developed: genetics was for fruitflies and the like. This changed irrevocably following the advances in recombinant technology in the 1970's and the seminal observation by David Botstein and others that polymorphisms in human DNA—irrespective of whether they had any function—would allow human disorders to be mapped, and subsequently disease genes cloned (11). The era of positional cloning was born, and in dermatology progress was kick-started by the independent discovery by Elaine Fuchs and Ervin Epstein that epidermolysis bullosa simplex was associated with mutations of the

basal keratins K14 and K5 (6, 12). The revolutionary idea was simply stated: by study of the co-segregation of genetic markers and a human disease phenotype, the causal gene for a disorder could be identified, in the complete absence of prior knowledge about pathophysiology (11).

The results of this revolution in dermatology grow ever larger. By the time you read this review the genes for several more genodermatoses will have been identified and the hectic pace of these 'molecular case-reports' will continue for several more years at least. Have these diseases been solved? Or, put in a less philosophical way, for that branch of applied biology that is dermatology, how significant are these discoveries? Whilst rejecting some of the hyperbole, particularly around subjects such as gene therapy (13), we would argue that these reports represent very real advances, although the distance between gene identification and therapeutic innovation shows little evidence of narrowing, an issue consistently ignored by those with little knowledge of clinical medicine. That the advance is real however we do not doubt. For instance dermatologists no longer find themselves in the intellectually embarrassing position of not knowing the function of the most abundant cellular proteins in their organ of interest; keratins. Imagine a haematologist only discovering ten years ago what function haemoglobin served. The unifying synthesis that genetics provides is easily overlooked. For example we cannot now think of the inherited mechanobullous or acquired immunobullous disorder without realising that the same molecules are targets in both types of pathogenesis (14). And even as we write this, molecular unity has spread to explain an infectious disease of skin, staphylococcal scalded skin (15). Furthermore in a heuristic bootstrap common to so much science, whilst you can't map a disease without an accurate diagnosis, when you have cloned the gene you can use this knowledge to further define clinical diagnosis and disease subgroups. Witness the reclassification of the inherited blistering disorders bringing a much needed order to what was once falsehood masquerading as complexity (16).

Genetically complex disease

No doubt, the achievements of Mendelian genetics are real and important. By contrast the field of complex genetic disease of skin seems murky and full of wishful thinking and inadequate analysis (10). The problem can be simply stated: in complex disorders the relation between gene and phenotype is poor, in genetic parlance, penetrance is low. Three papers published over the last year, although none primarily concerned with skin disease deserve our attention (7, 9, 10). First were the results of the large Scandinavian twin studies looking at common cancers (9). The conclusion from this important study confirmed what we already strongly suspected: by the criteria of twin methodology most human cancers have a low heritability. Cancer, contrary to what many believe is one of the least heritable diseases of man. The ever changing epidemiology of most human cancers reminds us that environmental influence should provide our

chief insight into cause and mechanism. In this context most human cancers will be little different from skin cancer or even the majority of inflammatory diseases of the skin.

The concept of heritability however is worthy of closer examination (17). An example may be more helpful than sterile definitions. In previous Scandinavian twin studies of basal cell carcinoma (BCC) the authors found that there was no need to include genetic factors in explaining the incidence of BCC in twins (18). Environmental factors appear more important. But heritability tells you about variation in a particular population not whether genes are important in pathogenesis. So for any population the heritability of a disease may be low but particular genes and their products may still be important rate limiting steps in pathogenesis. Imagine if the Scandinavian BCC study had been done elsewhere. In a population living on the equator comprising 50% pale-skinned Scandinavians and the other 50% Black Africans it would be bizarre if a large heritable component was not found. Now imagine a homogeneous population of Blacks in a similar location: low heritability. That there is little heritability does not mean that melanin is not a key step in preventing sun induced skin cancer—just look at albinos. Rather all heritability tells us is about allelic variation in a particular population. It says nothing about whether a gene and its product is a rate limiting step in disease pathogenesis. There is a general point here: identification of genes associated with psoriasis or other complex disorders is not the same as identification of targets for therapy or even of rate limiting steps in pathogenesis.

Prediction of disease risk

What of claims that the elucidation of the genetic determinant of complex diseases such as psoriasis or atopic eczema will allow prediction of disease risk or better identification of disease subgroups that may respond to a particular therapy. Again, Mendelian disorders provide the clear example of how this may work because of the strong relation between genotype and phenotype (i.e. high penetrance). In this sense you can view Mendelian disorders as complex diseases with extremely high odds ratios (>30). For common skin diseases assuming the common-allele-hypothesis these conditions do not apply. In a timely recent review in the *New England Journal of Medicine* Holtzman and Marteau modelled the relation between allele frequency, relative risk and predictive value (i.e. how often can you predict who gets a disease based on genotype) (7). For instance with a genotype frequency of 10% and a relative risk of 5—both reasonable or even optimistic estimates for many complex diseases—the predictive value is around 10% i.e. you are only right 10 times out of a 100. To raise the predictive value to over 90% requires rare genotypes (ω 1%) and risks of greater than 20. But this is more the domain of Mendelian or quasi-Mendelian disorders. Indeed for psoriasis, family studies would suggest a higher predictive rate based on simply asking subjects if their parents suffered from psoriasis rather than the genotyping of individuals.

Biology versus technology

There is one final issue to deal with. Much has been made of the power of new technological approaches, chiefly large scale Small Nucleotide Polymorphism (SNP) analysis to ‘solve’

complex diseases. But as has been pointed out the problem may be one of biology rather than technology (10). In our studies on red hair genetics SNP analysis and assumptions about linkage disequilibrium over a short area have proved hopelessly naive (3, 4, 19). Outwith the Mendelian disorders, given the evolutionary history of man and the ever changing environment it may well be a mistake to believe that the study of the complex genetic disorders will yield great insights in terms of disease prediction or therapeutic leads.

Conclusions

Are these views too pessimistic? We think not. Mendelian and quasi-Mendelian traits are rare but will offer robust insights onto pathogenesis, prediction, and possibly therapy. Current studies of complex diseases suggest however that familial clustering will be the result of a common environment, and a large number of low penetrant genes. We anticipate that the majority of allelic association studies will produce low odds ratios and be limited in applicability to the majority of human populations. Such studies identifying low penetrant allelic variation should not make us lose sight of other opportunities for identification of pharmacological targets or environmental triggers of disease.

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Tom Ha and Jonathan L Rees

Department of Dermatology,
University of Edinburgh, Royal Infirmary,
Lauriston Place Edinburgh EH3 9YW, United Kingdom.
jonathan.rees@ed.ac.uk