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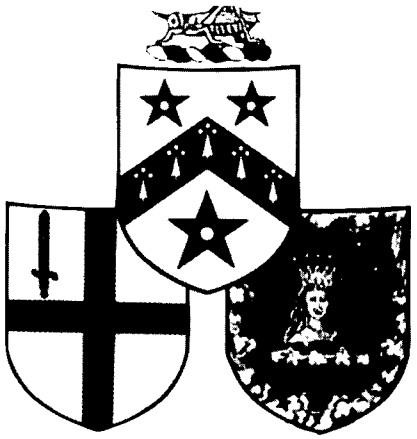

THE BIOLOGICAL CONSTRUCTION OF RISK: FROM MENDEL'S 'HIDDEN DETERMINANTS' TO DNA SEQUENCES

Second of Two Lectures by

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Gresham Lecture 5
The Biological Construction of Risk
Part 1: Genes beyond Mendel
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Up till now we have discussed genes, from Mendel to DNA, as if they were simple discrete units, beads on a chromosome string, so to say, lengths of DNA which coded for specific amino acids and hence specific proteins. In this model, genetic disorders and diseases occur because of specific faults in the DNA sequence - copying errors, mutations or whatever. One nucleotide base is substituted for another or deleted, the copying goes wrong and that protein can't be produced, or is wrongly made. So we get single gene disorders, phenylketonuria, Huntington's, sickle cell anaemia or whatever.
As we said last time, there are some 4000 such single gene disorders, mainly very rare, perhaps affecting no more than a few families in the UK. And these of course speak only of those gene disorders which are not so severe as to prevent a live birth occurring at all - many gene abnormalities are simply lethal - the embryo or foetus cannot survive.

For some of those single gene disorders which do permit live births, the consequences seem almost inevitable - the gene codes for a protein which is so important that almost nothing can overcome or mitigate its effects - eg Tay-Sachs, Lesch-Nyhan. For others - and that means most of them, however - just how the effects of the abnormal gene will play out during development remains less predictable. The genes which are risk factors for Alzheimer's disease - ApoE4 and presenilin - are examples. The reasons for this are pretty clear. There simply isn't a direct line between a gene and a character or a disease. The processes which lead from the single fused egg and sperm to the trillions of cells in the human body require the co-operative working of all the hundred thousand genes in our bodies. So if one gene goes wrong, so to speak, the effect is not like simply taking a circuit board out of a computer or a transistor from a radio. The remaining genes co-operate so as to minimise or mitigate the effect of the fault. Our bodies, especially during development, possess amazing powers of what is technically called plasticity - the capacity to repair or modify or find alternative ways to achieve their ends.

And this isn't all, because as well as the internal mechanisms that the body has to work to diminish the effects of faulty genes, there are external ones as well - the example we discussed last time, of phenylketonuria - changing diet to eliminate an amino acid which the genetic abnormality prevents us from metabolising - is one example. This is an extreme case of what we discussed in the last lecture as the 'norm of reaction' - the way in which the effects of any gene are profoundly affected by the environment in which the gene and the organism of which it is a part develops.

The consequence of all this is that there are multiple reasons why a person born with a particular set of genes may or may not contract a particular disorder. For most disorders, many genes, and many environmental and developmental factors, may predispose to the condition. Take Alzheimer's again as an example. The greatest risk factor for contracting the disorder is straightforward - age. The older you are, the more likely you are to get it. But then there are other factors as well - having had concussion or a general anaesthetic as a young person increases the risk. Women are at greater risk than men. Education, and active intellectual engagement later in life, diminishes the risk. And so on. And amongst these risks, having one form of the ApoE gene - ApoE4 - increases the risk, whilst having another form, ApoE2, diminishes it. But all along we are talking risks, increased or decreased chances of developing the disease, never certainty. And what is true for AD is true also for coronary heart disease, some forms of cancer and many many other conditions. Most of the conditions of our existence by which we live or die, are affected by a multitude of genes and environmental contingencies within which we steer a complex and distinctly non-linear route. Indeed, this is in the nature of living processes.

But this is only the start of the complexity. For we've still left you with the assumption, which is the way genetics was conceived of through all the time from Mendel to the 1970s, that genes are these linear sequences, lengths of DNA placed end to end along each chromosome, like so:

(Diagram)

But from the 1970s on it became clear that this was far from the case. The first puzzle was that there seemed to be far too much DNA in the human genome (or any other organisms, for that matter). It is estimated that our bodies contain some hundred thousand different proteins - if each protein is some 300 amino acids long and each amino acid needs 3 nucleotide bases to code for it this requires some hundred million bases - but the human genome contains three billion - three thousand million bases - the ones the human genome project is busy sequencing as we speak. So only about 1% of the DNA in the genome represents functioning genes. Some of the rest performs complex controlling functions, for sure, but the overwhelming majority has no known function - molecular biologists call it somewhat disparagingly junk DNA - or technically "intron" which stands for "intervening sequences." So the functioning genes are scattered very thinly indeed between all the rest of this junk.

(Diagram)

But it gets worse. For it then turns out that these functional genetic sequences aren't even complete genes, each coding for a complete protein. Instead there are lengths of coding sequence representing perhaps a fraction of a protein, separated by lengths of 'junk.' Each coding sequence is called an 'exon' by contrast with the introns.

(Diagram)

Using these sequences to code for proteins then becomes a very different matter from simply reading off a linear set of bases. The different sequences have to be assembled in the right order. Furthermore it then turns out that many different proteins can be made from the same set of sequences by shuffling the order in which the exons are assembled, or even missing some out.

That some such shuffling processes could occur was suspected back in the 1930s by Barbara McClintock, working with maize, when she came to the conclusion that genes could 'jump' from one part of the chromosome to another. Her observations were strongly resisted at the time as it went against the simple dogmas that people were working with - and it wasn't until the 1980s that she got her Nobel Prize for the work. However it is now clear that such jumping genes are part of the world of genetic complexity which is beginning to be uncovered. Genes - or exons - can jump not merely from one part of a chromosome to another, but from chromosome to chromosome.
The genome is not fixed, but is fluid. (Indeed - and we will come back to this in next year's lectures - genes or exons can cross from one species to another - so called horizontal gene transfer - which is a major problem in assessing the consequences of genetic manipulation).

What are the consequences of this new understanding of how genes function? Simplistic genetic determinism is even further reduced. We live in a world of probabilities, of risk factors, of uncertainties. And just how we are to live with such risks is the theme of the second part of this lecture, which is Hilary's section.

Risk and Anxiety in a Geneticised Culture

Risk, genomes and genomics Steven has been explaining the fluidity of the genome itself what I want to do is to explore some of the cultural constructions of risk, optimism and fatalism associated with both the old Mendelian genetics and the new genetics of the fluid genome.

1. First genetic optimism - the half-full cup-

This locates a nature nature distinction, which sees nature as the fixed given within us and nurture as outside - the environment which is around us and which in principle is subject to manipulation. If we can rearrange the outside - nurture - negative genetic predictions may be able to be regulated and diminished. This ties in with today's strongly held cultural beliefs that if we eat 'healthily', breathe clean air and drink clean water, exercise adequately etc. that we will prolong our lives and stay well. The

balance between individual responsibility and collective responsibility for the health promoting environment is a matter of intense eco- political debate. Nor is this a simple either/ or matter. Consumerist individual politics e.g. GM can have collectivist results Monsanto is ruined. Cf. Seattle or buying spring water. Nonetheless the genetic optimists (whether they follow and individual consumerist path or a collectivist path) assume that the better genetic risk is understood the better we can manage it.

2. Social Science Scepticism - the half empty cup.

As Steven pointed out there are currently some 4,000 single gene 'disorders' identifiable with DNA genetics - these range from the minor to the extremely severe. Diagnosing these Mendelian disorders increases our ability to 'predict' morbidity and mortality. Currently even for the most severe disorders there are no effective genetic therapies - though increased knowledge of the underlying biological mechanisms can and does lead to improved drug therapies. Otherwise the only therapeutic response is prenatal genetic diagnosis (PGD) to would be parents, and to pregnant women PGD and the offer of abortion.

The birth of medical ethics and post 1945 clinical genetics. How real is informed autonomous choice, the corner stone of post 45 ethics? ? Can we strengthen choice by making the values and pressures visible? Research points context (both macro and micro) as central: compare genetic counselling in a genetic clinic, versus in an ante-natal clinic and in most general practice. Clinical discourses of advice versus managing uncertainty. So support for patient making hard choices versus clear cut advice : lose weight, don't smoke while you are pregnant. Can we get non directive enabling counselling from health care professionals whom we go to for directive advice?. Does the proliferation of tests enhance rational risk assessment - see the optimists- or does it tend to generate a psychology of fatalism (Marteau Green Rose). As Green's survey of PGD questions - 'Harming or Calming?' How does social policy balance health service provision between genetic testing and care for people with genetic disorders. Ethics, efficacy of testing and value for the public health pound. PGD and eugenics- what are the messages about disability - e.g. to People with Downs or to a pregnant woman and her partner, that her foetus has Downs. The changing context of welfare provision, the family carries the burden of care the state and the family share the burden of care. Perception of risk to well-being of entire family modified by state support or the lack of it. How can we reconcile these comflicting pressures?

3. The New Genetic Quest - the genetics of common diseases.

The current genetics interest has moved on from Mendelian diseases to what are called "common diseases", not the common cold but cancer, heart disease - the major killers - but whose predisposing genetic causes are understood as polygenic. Genomics; Iceland, SKB, Humana and MRC/Wellcome. What is the core objective of this development? Is it about the extension of evidence based medicine so it will help the rational management of health care resources. But how do patients' benefit personally from this population based risk assessment? What do patients do with genetic information and the language of predisposition - we are only fairly not very rational in our self health care see smoking and drinking. Clearly the lottery says that culturally probability theory is not well grasped, but does tell us that hope is extremely human, And how does this bringing together of genotype (genetic profile) phenotype (the medical record) tie in with concepts of the fluid genome? How can the dynamic complexity of the latest genetics tie in with what seems to be a static reading of nature and nurture. Or have I misread the genetics in the new genomics? So from the social scientist more questions than answers.

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