the deeper genome

Why there is more to the human genome than meets the eye

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INTRODUCTION

How the Genome Lost Its Junk

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> 'Sit down before fact as a little child, be prepared to give up every preconceived notion, follow humbly wherever and to whatever abysses nature leads, or you shall learn nothing.' *Thomas Huxley*
>
> 'What is a scientist after all? It is a curious person looking through a keyhole, the keyhole of nature, trying to know what's going on.' *Jacques Cousteau*

It was on the morning of 5 September 2012 that I first heard about the death of 'junk' DNA. I was sitting at a desk at *The Times* newspaper in London; to one side, through huge windows, I could see the Thames, Tower Bridge—which all summer had been sporting the Olympic and Paralympic symbols—and beyond that the Shard, the London Eye, and other famous landmarks. Above me, in the open-plan building occupied by Rupert Murdoch's News International company, was the floor occupied by the *Sun*, with its huge, framed past front pages with headlines like 'Up Yours Delors!' and 'Sling Your Hook!', references to European Commission President Jacques Delors and radical Muslim cleric Abu Hamza, respectively. At the time the *Sun* was embroiled in a major investigation into its alleged use of illegal phone tapping.[1] Although it was 9.30 a.m. the offices were still largely empty; the deceptive lack of activity was contradicted, however, by the influx of messages in my e-mail inbox from other journalists, pitching ideas to the editors for the day's stories even as they travelled to work by the Underground or rail.

Although I'd been working at *The Times* for over a month, my position funded by a British Science Association Media Fellowship,[2] I still felt a bit of an imposter, perhaps because the day-to-day activities of being a journalist were so different

compared to my normal role as a biologist and lecturer at Oxford University. One particular difference was the tempo; while in my regular job I may spend months, even years, gathering data for a study and presenting it for publication, submitting the manuscript to a journal, and then spending more time battling with anonymous reviewers who can either damn the whole study with a dismissive word or demand further data, here the pace of publication was very different.

So a typical day at *The Times* began by scouring Eureka Alert and other websites that gather together the latest press releases, funding announcements, and other news from the world of science.[3] This would form the basis of my day's pitch to the news editors, which typically would consist of two, maybe three, stories I thought might compete with other news from the world of politics, economics, sport, and scandal. After anxiously waiting while the editors had their mid-morning meeting, I would hopefully get the go-ahead to write 600 words on one topic, 400 on another, all to be submitted to the news desk by 3 or 4 p.m. to have any chance of making the printed paper. Around me, kick-started into life by similar demands, the office was now a whirring hub of activity as everything became subsumed towards a central goal—the production of the next day's news. If I had written well, and, as important, proved lucky against competing news items, I might see one or two of my articles online by early evening. However, the real test of how well I was doing would be seeing a piece that I'd written appear in next day's print edition. And then, like rubbing clean a slate, the next day kicked off exactly the same way.

This morning, however, it was clear something odd was afoot. Over a dozen different press releases had appeared on Eureka Alert, all from different research institutions, but all mentioning ENCODE—an acronym for ENCyclopedia of DNA Elements. As I read further, I learnt the reason for this sudden burst of information: ENCODE was the culmination of almost a decade's research involving 442 scientists from 32 institutions and costing $288 million.[4] And its claims seemed as big as its budget. So while the original Human Genome Project provided the sequence of letters that make up the DNA code, ENCODE appeared to have gone substantially further and told us what all these different letters actually do. Perhaps most exciting was its claim to have solved one of the biggest conundrums in biology: this is the fact that our genes, which supposedly define us as a species, but also distinguish you or I or anyone else on the planet from each other, make up only 2 per cent of our DNA. The other 98 per cent had been

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written off as 'junk'; however, this raised the question of why our cells should spend vital energy replicating and storing something with no function. The existence of so much junk DNA had also featured heavily in debates between evolutionists and creationists, for why would any creator design a genome in which only 2 per cent actually works?

Now, as I read though, I found that ENCODE's new findings, all synchronized to appear simultaneously in 30 linked publications, had a new and excitingly different take on this matter. By scanning through the whole genome rather than just the genes, and using multiple, cutting-edge approaches to measure biochemical activity, ENCODE had come to the startling conclusion that, far from being junk, as much as 80 per cent of these disregarded parts of the genome had an important function. Indeed, for Ewan Birney of the European Molecular Biology Laboratory near Cambridge, the charismatic spokesperson of the project, this was probably an underestimate, since it was 'likely that 80 percent will go to 100 percent. We don't really have any large chunks of redundant DNA.'[5] The path-breaking nature of the project was emphasized by another ENCODE researcher, John Stamatoyannopoulos of Washington University in Seattle, who predicted that the findings would 'change the way a lot of concepts are written about and presented in textbooks'.[6] Perhaps most excitingly for a general audience, ENCODE also claimed that its findings were casting important new light on links between the genome and common diseases such as heart disease, diabetes, auto-immune conditions, and mental disorders like schizophrenia.[6]

Clearly, this seemed like big science at its best, and, as such, I co-wrote a story with Tom Whipple for *The Times*, in which we spelled out the study's implications. It appeared in the following day's paper entitled 'Rummage through "junk" DNA finds vital material'.[7] Similar positive assessments of the new findings appeared in media outlets across the world, all of which repeated the project's main conclusion that the idea of 'junk' DNA had been overturned by the discovery that as much as 80 per cent of the genome had an important function.[8,9,10] This was also the message from serious science journals such as *Nature* and *Science*, with the latter headlining the discovery 'ENCODE project writes eulogy for junk DNA'.[11]

By the end of my six-week placement at *The Times*, I'd published a total of twenty-two stories and features, on topics ranging from why chocolate is addictive, the discovery of the oldest tooth filling in history, and whether becoming a eunuch would make men live longer, to the burning question of whether a

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potential super-volcano is lurking under the city of Naples.[12] But the story that most resonated for me on a personal level was the ENCODE findings. I resolved to find out more about their implications, not just for my own research, but also with regard to the much bigger question of how our genomes define us both as a species and as individuals. Most intriguing was the controversy that erupted a little while after the ENCODE findings were published. So an article published in the journal *Genome Biology and Evolution* in February 2013, attacked the findings in a vitriolic tone not normally associated with scientific debate, or at least not in the pages of an academic journal.[13] According to the article, the claims of ENCODE were 'absurd', its statistics 'horrible', and it was 'the work of people who know nothing about evolutionary biology'. And in a subsequent interview, lead author, Dan Graur of Houston University, said 'this is not the work of scientists. This is the work of a group of badly trained technicians.'[14] A central criticism was that ENCODE researchers had confused activity with functionality. 'Just because a piece of DNA has biological activity does not mean it has an important function in a cell,' said Graur. 'Most of the human genome is devoid of function and these people are wrong to say otherwise.'[14]

In contrast, there was the view of John Mattick of the Garvan Institute of Medical Research in Sydney, who argued that the ENCODE leaders were, if anything, too conservative in their claims, and that the findings showed 'we have misunderstood the nature of genetic programming for the past 50 years'.[15] Another proponent of this view, Evelyn Fox Keller of the Massachusetts Institute of Technology, believes recent 'genomic science has changed the very meaning of the term, turning the genome into an entity far richer, more complex, and more powerful—simultaneously both more and less—than the pre-genomic genome, in ways that require us to rework our understanding of the relation between genes, genomes and genetics'.[16]

So who is right? I resolved to find out, and this book is partly a result of that quest. However, while my interest in writing this book began with ENCODE, it has subsequently grown to encompass a much wider field of enquiry, all relating to the topic—how do our genomes make us human? This is a question that often comes up in the lectures and tutorials I give to medical and biology students at Oxford University in which we discuss the genetics of disease; for instance, why are some people more susceptible to certain disorders than others? But it also flows from a long-standing personal interest in what distinguishes humans as a

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species, but also as individuals. Unfortunately, for some time now I've been dissatisfied with the available explanations as to how our human genomes work, on the one hand to distinguish us from other species on the planet, and on the other to create the unique mix of personality, capabilities, needs, desires, and susceptibility to illnesses and disorders, that define us as individuals.

As a child, I remember being fascinated by my parents' copy of *The Naked Ape*, by Desmond Morris. This book became a publishing sensation in the 1970s with its claim that modern human behaviour and society was largely rooted in instincts that had evolved in the Stone Age.[17] There was a problem though, in that Morris's take on prehistoric life was about as accurate as the 1950s cartoon *The Flintstones*, or the '60s film *One Million Years* BC starring Raquel Welch. However, what *The Naked Ape* lacked in authenticity was more than compensated by its numerous references to sex, which, to someone just reaching puberty, were almost as alluring as Welch's animal skin bikini. For a teenage boy just starting to worry about my attractiveness to the opposite sex, being told that humans not only have the largest brain compared to body size, but also the largest penis, making them the 'sexiest primate alive',[18] was sweet music to my fragile ego. Meanwhile, learning that humans' fleshy ear lobes, unique to our species, are erogenous zones, or that women's breasts are an important sexual signalling device rather than simply providing milk for babies,[19] was definitely something for my newly hormone-stimulated brain to chew over. And finally, Morris's claim that monogamy evolved so that men out hunting could trust their mates were not having sex with other men, and that human 'nakedness' helped intensify pair-bonding by increasing sensory pleasures,[19] were all food for thought to a teenage mind.

Unfortunately, as scientific fact such claims were about as substantial as Welch's bikini, although they could possibly be excused by a lack of understanding of human evolution and its molecular and cellular basis at this time. Yet what is surprising is how little many 'biological' explanations of human behaviour and society have changed since the 1970s. Take, for example, a recent book about human culture by Mark Pagel of Reading University, which moves in a few pages from self-sacrifice in amoeboid slime moulds to what Pagel calls a 'helping gene' that codes 'for an emotion that disposes people to be friendly'.[20] This sounds quite nice except this helping gene's influence only extends to people of the same nation; towards other national groups it becomes the 'jingoism' or 'xenophobia' gene. The author ends by saying 'next time you feel that warm nationalistic pride

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at the sound of your national anthem or the news of one of your country's soldiers' valour, think of the amoebae!'[21]

One problem with this argument is its assumption that all members of a nation state behave in a similarly patriotic manner. So it fails to explain why millions of people in Britain opposed their government and marched against the recent wars in Iraq and Afghanistan.[22] But a more fundamental difficulty is that the proposed 'gene', which somehow manages to combine both nice and nasty characteristics, is a complete figment of the author's imagination. And, lest this be seen as an isolated incident, I could point to a range of other examples in which single genes are said to determine intelligence, personality, and even men's supposed unwillingness to do the ironing, without scientific evidence to back up such claims. In fact, for all the lip service paid to genetics in such accounts, the 'gene' here might as well be made of green cheese given the lack of any real attempt to engage with actual molecular mechanisms rooted in the real genome.

Actually, this is not quite true. The claim that homosexuality is due to a 'gay' gene, which made headlines across the world in 2003, was based on a study published in the prestigious journal *Science*. Evidence was presented that gay men had specific differences in a region on the X chromosome, Xq28, that was claimed to be linked to their homosexuality, and passed down through the mother.[23] What followed was a huge debate about the implications of the discovery. In the gay community itself reactions ranged from fears that screening programmes might identify and abort 'gay foetuses' on the basis of their possession of the gene, to those who thought the discovery would scientifically 'legitimize' homosexuality and therefore help end gay oppression, although this ignores the fact that the clear biological basis of skin colour has not prevented oppression based on this difference.[24] Such was the publicity around the discovery that a T-shirt with the slogan 'Xq28—thanks for the genes, Mom!' became a popular item in many gay bookstores. Missing from much of the coverage, however, was that what had been discovered was not an actual gene but merely an association with a DNA region on the X chromosome. And two decades later, the authors have failed to identify such a gene, while attempts to reproduce the findings by others have been equally negative, leading to suspicions that the original 'discovery' was just a statistical artefact.[25]

Such failed attempts aside, one undoubted reason for the popularity of accounts of human behaviour and society that make no attempt to engage with

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actual molecular mechanisms, is that they tell entertaining 'just-so' stories about human evolution without having to bear scrutiny as to whether such stories are actually true. In this sense, as science journalist Tim Radford has noted, the 'gene' here is not so much a real object as a 'metaphor, an analogy, an "as if", a useful way of thinking about how behaviours, strategies and responses might have emerged'.[26] Now while I'm all for metaphors as a way of making complicated scientific concepts comprehensible, a problem arises when these get in the way of a true understanding of the material basis of nature. Taking an example from the physical sciences, the initial model of the atom proposed by Ernest Rutherford in 1911 pictured it as a miniature solar system, with electrons orbiting the nucleus just as our own planet orbits the Sun; however, subsequent studies showed that this metaphor was far too simplistic. Surprisingly, in the biological sciences far too many popular accounts are still anchored in an old-fashioned view of genes that either sees them as abstract units with no material form, or if they do acknowledge this link, subscribe to the crude picture of genes as 'beads on a string', discrete and isolated entities on each chromosome.

In contrast, while in this book there will be plenty of speculation about the link between genes and what it means to be human, my aim will be to make sure this is always backed up with evidence of real molecular mechanisms based on the most cutting-edge studies of the genome. Here, though, we face a problem. While key individuals involved in the Human Genome Project, such as Sir John Sulston of the Sanger Institute near Cambridge, promised that, 'for the first time we are going to hold in our hands the set of instructions to make a human being',[27] and British Science Minister Lord Sainsbury said 'we now have the possibility of achieving all we ever hoped for from medicine',[27] the reality has been rather different. So when scientists sought to use the genome to identify links between differences in the DNA code and common disorders like heart disease, diabetes, and mental conditions like schizophrenia, bipolar disorder, and autism, the problem was not finding genetic links to these disorders but rather the astounding number of these.[28,29] Instead of identifying just a few strong genetic links with each condition, as had been commonly predicted, scores or even hundreds of such links have been made, with each only apparently contributing a tiny amount to the chance of succumbing to these disorders. Such findings seem to mock the idea that we can find meaningful, and useful, links between our genomes and such conditions, and if true for disease, surely it must be more so for other aspects of being human,

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such as our unique personalities and capabilities. This has led one critic of the genome project—neuroscientist Steven Rose of the Open University—to argue that 'they said this was the greatest achievement since landing a man on the moon. One even said it ranked with the discovery of the wheel. And yet none of this cornucopia of benefits has come out of it.'[30] Another critic, bioethicist Tom Shakespeare of Newcastle University, has said 'we share 51 percent of our genes with yeast and 98 percent with chimpanzees—it is not genetics that makes us human'.[27]

In this book, my aim is to find a middle way between the view that the complexities of the human condition can be reduced to simple, hypothetical 'genes' without any mechanistic underpinning, and the opposite view that sees things as far more complex, yet rejects the idea that we have learned anything useful from the genome project, about both the diseases that afflict us as a species, and what it means to be human. In so doing, I will be drawing on many years of experience studying genes and how they function. In my quest to understand how cellular signals regulate important bodily processes, I have isolated and characterized novel genes and studied their functional properties in a test tube and in cultured cells, but also what happens when their activity is inhibited or altered in a living animal. This has allowed me to appreciate the power, but also limitations, of the so-called 'reductionist' approach to biology.

Such an approach aims to understand complex biological systems by dissecting them into their constituent parts, or as Francis Crick, co-discover of the DNA double helix put it, 'to explain all biology in terms of physics and chemistry'.[31] The power of this approach was demonstrated to me when my colleagues and I used it to show that a single gene codes for a protein in the sperm which triggers the chemical signal in the egg that stimulates embryo development.[32,33] However, while studying the role of genes in the living organism, I have also increasingly come to realize the complexity of their behaviour. A common method for studying how genes work and their function within the body is to breed animals in which the action of a particular gene is inhibited by genetic engineering, thus creating a 'knockout' mouse.[34] Such animals have become very important 'models' of human disease. Yet, surprisingly, in many cases abolishing a gene's activity has little effect on the whole organism, or leads to opposite or very different effects than predicted based on its properties in a test tube or in cells in a culture dish. Such unexpected findings are often said to be due to

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'compensation' by other genes during embryo development but this is really just a hand-waving gesture to convey the fact we often know very little about why particular genomic manipulations have unforeseen effects.[31] What these findings do suggest is that while isolating the effects of one gene from others in the body can lead to important insights, ultimately, gene action can only be properly understood as part of a wider whole. And if true for a mouse how much more so for humans, with our complex behaviour and culture driven by social innovation as much as by biology.

So does this mean that attempts to find genetic links to the complexities of human behaviour and society are doomed to failure? In this book I intend to show this is far from the case, but I also want to challenge some long-held assumptions in biology: one being the idea that genes can be treated in isolation, and also the very definition of what we mean by a gene. To do this I will not only explore what the ENCODE findings have to tell us about this question, but also investigate what I believe is a more general shift taking place in our perception of the genome and how it works. Importantly, this shift is based on new technologies that mean that, rather than studying single genes in isolation as previously, we can now observe changes in the activity of the genome as a whole.[35] This analysis can extend both to a whole organ like the human brain, but also allows us to study how genes are switched on and off, in real time, in a living cell, something undreamed of only a few years ago.[36]

Based on the findings emerging from the use of such technologies, I will look at important new developments like the increasing recognition that, far from simply being a linear code, the genome only really makes sense as a 3D entity.[37] Moreover, this 3D entity dynamically changes in response to signals originating both from within, and outside, the cell. Another important development is the recognition that RNA, DNA's chemical cousin, plays a far more important role in the cell and organism than previously thought.[38] So instead of simply being a messenger between DNA and proteins—the building blocks of the body—RNA is proving to have a multitude of other key roles, and on a much vaster scale than could have been imagined. Finally, new evidence is emerging that, far from being a fixed DNA 'blueprint', the genome proper is a complex entity that includes proteins, and both the DNA and these proteins can be chemically modified in a far more rapid, and reversible, fashion than suspected.[39] This makes the genome exquisitely sensitive to signals from the environment, and challenges the idea that

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life is merely a one-way flow of information from DNA to organism. Perhaps most surprisingly, the genome's status as a structurally stable unit is being called into question, with evidence that certain genomic elements have an ability to move about, sometimes to the detriment of normal cellular function, but also acting as a new source of genome function.[40,41,42]

Excitingly, while the significance of such phenomena for long-term evolutionary change remains controversial, there is increasing evidence that these newly recognized features of the genome may have played a fundamental role in the emergence of *Homo sapiens* as a unique species with self-conscious awareness and the power to transform its environment in a way that sets it apart from all other life forms on the planet.[43] This focus on human beings will be an important theme of this book, for although I will show how studies on organisms ranging from the humble bacterium to our closest living animal cousins, chimpanzees, have transformed our understanding of human biology, ultimately it is with our own species that I will be most concerned. And I will be aided in this task by the fact we can now study the genomes not just of living primates, but also extinct proto-human species like Neanderthals.[44,45] In addition, it is becoming increasingly feasible to determine the complete DNA sequence of genomes, as well as chemical modifications of this DNA and its associated proteins, from large numbers of living human beings.[46]

Before tackling these important new reconsiderations about the genome though, I first want to take us back in time to look at how scientists came to understand how living things appeared on Earth, what led to the diversity of life we see around us, and how genes and genomes mediate this process. In so doing we will reach back into the lives and times of famous scientists like Darwin and Mendel, but also lesser known figures whose theories and findings have nevertheless enriched our view of the cell and organism. Having thus developed a secure foundation based on what, until recently, constituted the 'orthodoxy' in this area of science, we will examine how this orthodox view is currently being challenged. Using such new information we will seek to understand what this can tell us about abnormalities of the human condition, not just 'single-gene' disorders, but also more common disturbances, such as heart disease and diabetes, and also mental conditions like schizophrenia and bipolar disorder, that afflict millions of people across the world. In particular, we will investigate whether the genetic complexity that appears to underlie these disorders mean that attempts to

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identify new methods of diagnosis and treatment are fatally flawed, or if there is a path to a new understanding of these conditions despite this complexity. Finally, we will explore how such new understanding of the genome is being used to address a key remaining question for humanity, namely what is so special about our own species that led us to such a primary position on Earth. With all that in mind, it's time to begin our quest. But first, a personal question—do you feel lucky?

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