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Genetic Confusion

The patient was a tiny baby, just 2 days old, breathing abnormally fast. Eventually things settled down and the baby was sent home. But in the months that followed, her parents kept bringing her back to A&E with severe breathing difficulties and blood that was abnormally acidic. Each time, a tiny sample of blood was taken for tests. What might be going on?

The year was 1984 and this was the National Unit of Human Genetics at the American University Hospital in Beirut, Lebanon. I had gone there a few years earlier to set up a new laboratory of biochemical genetics as part of the Unit. This was a country where consanguineous[1] marriages between first cousins were common. But this little baby came from non-relatives and there was no clue from the family history as to what might be happening. There can be a myriad of reasons for abnormally acidic blood ('lactic acidosis'). The first two times the baby was brought to A&E, the enzymes we tested turned out to be normal.

This was followed by more hours in the library searching the literature (no online digital resources in those days!). Could it possibly involve a very rare deficiency of fructose 1,6-diphosphatase? This is an enzyme required for breaking down fructose – a sugar found especially in honey and mature fruit – essential for making cellular energy from the fructose. Without it, fructose is converted to lactic acid, so acidifying the blood. We set up the test using leucocytes (white blood cells) from control blood, ready for the next opportunity. Sure enough, the baby was soon back in A&E again and this time we nailed it: the fructose 1,6-diphosphatase levels in the baby's blood were barely detectable – problem solved, only the thirty-ninth reported case in the world (Alexander et al., 1985). It turned out that, due to her failure to thrive, anxious relatives had been dosing the little girl with honey –

unwittingly nearly killing her in the process. All that needed to happen was for the girl to be placed on a low-fructose diet and all would be well.

I have sometimes wondered what happened to that little girl, who must now be a woman in her mid-30s. Did she get married and have a family? Has she kept to her diet and so maintained her good health? Of course, her samples were (quite properly) all anonymous when they arrived in the laboratory, so I will never know. She was from a Sunni Muslim family. Less fortunate was a baby boy aged 18 months who presented at the hospital around the same time with convulsions followed by irreversible coma and death on his sixth day in hospital. He was the first child of consanguineous parents from the Lebanese Druze community. His fructose 1,6-diphosphatase was also deficient (Alexander et al., 1985). Two of his first cousins, also the product of a consanguineous marriage, had previously died at the age of 2 years. Had it been possible to detect their deficiency within the first few months of life, they would all be alive today.

Outside the hospital walls, the Lebanese civil war continued to rage and hundreds were dying. But genetically there were winners and losers as well. And in some cases, at least, if only the consequences of the genetic defect could be identified early enough – in this case an absent enzyme – then it meant life rather than death.

1.1 Mendel's Inheritance

To understand how the enzyme deficiency detected in those Lebanese babies is passed on through families, we need to go back to an Augustinian Moravian monk named Gregor Mendel (1822–1884). In the sheltered space of St Thomas's Abbey in Brno (now in the Czech Republic) where he was friar and abbot, Mendel carried out a painstaking series of breeding experiments in which he bred nearly 30,000 pea plants of carefully selected varieties.

Mendel's experiments revealed several key findings. The varieties of pea plants that he started with bred true for many generations. Today, we would say that they were genetically pure lines. This was an important factor in his success. When Mendel cross-hybridised these different varieties, the traits inherited by the next generation of peas (the 'hybrids') were 'particulate' – their seeds were either wrinkled or smooth, or the plants were either tall or short. The hybrids showed only one of the two possible character traits present in the parents, inconsistent with the idea of 'blending inheritance' in which different traits merged with each other. Mendel also noticed that some traits were 'dominant' and some were 'recessive'. When he crossed the tall pea

plants with the short pea plants, the ratio of tall to short plants after two generations came to approximately 3:1 – tall was a dominant trait and short was a recessive trait. But if he crossed tall with tall, he got only tall plants, and likewise short with short yielded only short plants. Experiments with peas having multiple different characters suggested that each trait (e.g. height, colour, texture) was inherited independently through subsequent generations.

Mendel's 'particles' that led to the inheritance of discrete characteristics in his pea plants are what we now call genes, and it is what we now call the 'Mendelian Laws of Inheritance' that allow us to understand what was going on in the Lebanese family just described. Figure 1.1 shows the pattern of inheritance of the defective gene in this family. Today, there are around 7,000 known 'Mendelian' genetic disorders,[2] meaning medical conditions that are caused by a defect in a single gene with a pattern of inheritance like that shown in Figure 1.1. But they are mostly rare, many extremely rare, and taken together represent only a few per cent of the diseases that afflict humanity.

In practice, the development of all the major diseases that impact our lives, such as cardiovascular disease, psychiatric disorders and some cancers, is influenced by hundreds of variant genes that operate together to generate higher or lower levels of risk. Each variant gene looked at individually is

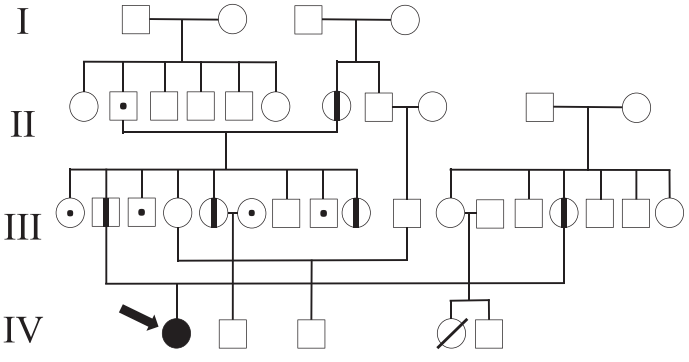

Figure 1.1 Pedigree of a Lebanese family showing the inheritance of fructose 1,6-diphosphatase deficiency. Roman numerals I–IV refer to generation number. Circles represent females and squares males. A symbol with a thick black vertical line indicates heterozygotes (carriers) and the solid black circle indicates the homozygous (two defective genes) patient with the deficiency. A dot in the middle of a square or circle indicates that this individual was tested and found to have normal levels of fructose 1,6-diphosphatase. A line through a symbol means 'deceased'. From Alexander et al. (1985).

inherited just as Mendel described, but in practice they are coordinating together as one big system to bring about various effects in our bodies.

The system as a whole is now referred to as our 'genome'. This term refers to the sum total of all the information encoded in our DNA. We'll consider how the coding takes place in Chapter 2. But for the moment it's worth noting that our genomes are like huge recipes and, just as in the recipe for a cake, all the ingredients have to coordinate together to produce the final product. We wouldn't say that one particular component in the recipe causes the cake to be either wrinkled or smooth, just to pick up on Mendel's language; we would say that it was the recipe as a whole, together with the particular oven temperature, that was the cause.

This illustrates some of the problems that can arise from learning Mendel's laws in school biology. If we start our education in genetics by thinking that 'one gene leads to one characteristic', this can spill over to how we think about genetics in general. Such an idea is reinforced by precisely the kind of medical situation illustrated in Figure 1.1. An error in a single gene causes a potentially lethal disease, which arises from not being able to digest fructose properly. This sounds like one gene leading to one particular fault in the system – which is true, although in fact the disease system in this case is quite complicated with many steps.

Here again the cake metaphor might help: if, for example, we mistakenly leave the baking soda out of the recipe, then the post-oven result will be a dense mass with a heavy texture, not a cake. So a single recipe error leads to a complex developmental process with an unfortunate outcome. This happens with genes as well – an error in a single gene can result in a complicated chain of events that leads to a big difference in the eventual outcome. But the key word here is 'difference'. The single variant gene does not encode the whole characteristic – the final outcome – but it does make a big difference to the outcome. As we'll see later, genes as 'difference makers' is a really important concept when it comes to thinking about the role of different genes in variant human behaviours.

The unfortunate fact is that the way biology is taught in schools spills over into the public understanding of genetics, and the idea that one gene causes a particular human characteristic, even in quite a deterministic kind of way, is still all over the place in the media, as the following section illustrates.

1.2 The Media Portrayal of Genetics

One common media confusion is the idea that there is a 'gene for' some complex human characteristic. There are mean genes, gluttony genes,

gangster genes, liberal genes that cause you to read *The Guardian* and even the whimsical suggestion of a 'geneticism gene' that predisposes some people to think that behaviour is caused by genes. Some sample media headlines illustrate the point: 'Reason to be cheerful: happiness gene is in Britain's DNA' (*The Times* front page[3]); '"Binge-drinking gene" discovered' (BBC News[4]); 'Study links spread of religion with "believer gene"' (*Huffington Post*[5]); 'Study shows how to tell if that man in your life has caring genes' (*Digital Journal*[6]); 'Teen survey reveals gene for happiness' (*New Scientist*[7]); 'The science of stress – does your child have the "worrier" gene?' (*The Times*[8]), 'Exam success may be due to a handful of genes' (*The Times*[9]) and so forth.

An interview with the singer Sinead O'Connor was headlined with a quotation from the singer: 'I have no shame. I don't have an embarrassed gene' (*The Times*[10]). In 2006, an Australian Associated Press article began by stating that 'New Zealand Maori carry a "warrior" gene which makes them more prone to violence, criminal acts and risky behaviour, a scientist has controversially claimed' (Kowal and Frederic, 2012). Even sober academic journals such as *Nature* can seemingly not resist the temptation to compress a complex genetic finding into such attention-grabbing headlines as '"Ruthlessness gene" discovered' (Hopkin, 2008) or 'A gene for impulsivity' (Kelsoe, 2010) even though the authors of the scientific papers whose work is being publicised studiously avoid such language. Discussing the tendency that many people drink alcohol at times of stress, *Newsweek* reassured readers that 'if this is you, don't blame yourself. Blame your DNA.'[11] Another widely read newspaper asks: 'Could it be that binge eaters really can't help themselves? A new study says that weak genes – not weak willpower – may be the reason some people compulsively overeat.'[12]

The general impression given is that it's the genes that run the show and so there's not much you can do about it. Although science journals are generally more careful in their language, their news reporters occasionally slip up and give a similar impression. A news feature in the top scientific journal *Nature* illustrates this point well, entitled 'The anatomy of politics – from genes to hormone levels, biology may help to shape political behaviour' (Buchen, 2012). The author writes that 'An increasing number of studies suggest that biology can exert a significant influence on political beliefs and behaviours', reporting that 'genes could exert a pull on attitudes concerning topics such as abortion, immigration, the death penalty and pacifism'. In the article, John Hibbing, a political scientist at the University of Nebraska-Lincoln, is quoted as saying that 'it is difficult to change someone's mind about political issues because their reactions are rooted in their physiology'. In this report, genes

and physiology are seen as something different from 'us' and 'our mind', and they seem to be controlling us, so we cannot even change our mind.

Political commentators and historians appear to find genetic explanations for cultural and political differences particularly alluring, perhaps because their grasp of the genetics does not match their expertise in other academic disciplines. In his book *A Farewell to Arms* (2007), the economic historian Gregory Clark argued that the English came to rule the world because the rich outbred the poor, so contributing more of their 'superior' genes to the conquering nation. In 2014, *A Troublesome Inheritance – Genes, Race and Human History* by Nicholas Wade stirred up a hornets' nest with the suggestion that genetic differences between 'the three major races' help to explain economic differences between races and 'the rise of the West'.[13]

But even experts in the field of genetics can inadvertently stir up a minor hornets' nest with the kind of language used in their popular books. Leading behavioural geneticist Robert Plomin from London's Institute of Psychiatry (where I did my PhD incidentally) faced a minor storm with his book *Blueprint* published in 2019, writing that 'DNA is the major systemic force, the blueprint, that makes us who we are. The implications for our lives – for parenting, education and society – are enormous' (Plomin, 2018). The social implications are barely spelt out in Plomin's book in any detail, except in a rather speculative and futuristic kind of way, but the 'blueprint' metaphor is a powerful one and does seem to imply a rather deterministic role for our genetic endowment. Such an impression is certainly reinforced by comments such as 'Nice parents have nice children because they are all nice genetically' and 'DNA isn't all that matters but it matters more than everything else put together.' All this led a reviewer of *Blueprint* in the journal *Nature* to claim that 'It's never a good time for another bout of genetic determinism, but it's hard to imagine a worse one than this' (Comfort, 2018). Strong words indeed, but an indication of how passions run deep in this particular field. Another recent article in *Nature* comments: 'The DNA-as-blueprint model is outdated, almost quaint' (Comfort, 2019).

My own choice above of the 'recipe' metaphor could easily be misinterpreted as leading to a type of genetic determinism, although its aim is precisely the opposite: to communicate the many ways in which small variations in the composition of the recipe and the environmental conditions involved in the development of the cake (known as 'cooking') lead to very major changes in the final product. But metaphors and images are powerful and can exert a strong influence over the ways in which we think about things.

Another book that came out in 2019 also uses a title that readily lends itself to viewing the influences of genes through a deterministic lens. *The Science of Fate* by Hannah Critchlow (Critchlow, 2019) surveys the role of genetic variation in influencing our futures, with a focus on health and disease. Nothing wrong with that – this book will do the same in the context of human behaviour – but the problem comes with the way the material is slanted in a fatalistic direction. Small wonder that a review of the book in *The Times* was headlined 'Relax, you have no free will' with the subtitle 'Science shows that everything from your flabby tummy to your political views is preordained.'[14]

The first announcements of the complete sequencing of human DNA in the early 2000s provide a fertile hunting ground for other powerfully influential metaphors. Descriptions such as 'the Holy Grail', 'the Book of Life' and 'the Code of Codes' were all used. Walter Gilbert, who first used the phrase 'Holy Grail' to describe the genome at a conference at Los Alamos in 1986, and who was one of the foremost promoters of the Human Genome Project, described its potential with this graphic image: '[O]ne will be able to pull a CD out of one's pocket and say, "Here is a human being; it's me!" . . . To recognize that we are determined, in a certain sense, by a finite collection of information that is knowable will change our view of ourselves. It is the closing of an intellectual frontier, with which we will have to come to terms' (Gilbert, 1992). No equivocation there. In 2012, the first wave of thirty papers reporting the results of the ENCODE project were published. ENCODE stands for the 'Encyclopedia of DNA elements' and aims to map all the functional sequences of the human genome. The main introductory paper in this series begins its Abstract by emphasising that the 'human genome encodes the blueprint of life' (Dunham et al., 2012), again the same powerful metaphor describing how DNA works. The genome in popular scientific literature is often referred to as 'an instruction manual', giving the impression that the human body is assembled from the manual much as you might put together a piece of furniture from the kit supplied.

We also note the ways in which the phrase 'it's in his/her DNA' has come into common usage in all kinds of contexts, some rather odd. As Brad Pitt once told the *Daily Mail* while discussing US gun control: 'America is a country founded on guns. It's in our DNA.'[15] 'Diamonds and Antwerp – it's in our DNA' declares a website from Antwerp wishing to sell diamonds.[16] The cloud computing service provider Oxygen assures us that 'for Oxygen, security is in our DNA. The security of you and your company's data will always be our priority.'[17] In commenting on a new TV drama series, the Director-General of the BBC was quoted as saying that 'Drama is something

that is in the lifeblood of this country and in the DNA of the BBC too.'[18] The presumed implications of such language are clear: what is in the DNA must be immutable and unchangeable – somewhat missing the point that our DNA is undergoing a constant process of change and diversification.

1.3 Genetic Testing and Genetic Determinism

The proliferation of direct-to-consumer (DTC) genetic testing companies has also contributed to the idea that it is our genes that are pulling the strings of human destiny. The front page of *The Guardian* in 2019 proclaimed that 'IVF couples could be able to choose the "smartest" embryo: US scientist says it will be possible to rank embryos by "potential IQ" within 10 years.'[19] This was based on comments made by Stephen Hsu, Senior Vice President for Research at Michigan State University, but who is also co-founder of a company called 'Genomic Prediction', which – no surprise here – might well be offering such a service over the coming years. As we shall see later, the relationship between genetic variation and intelligence (which itself has many different definitions), is highly complex, and the claim made in *The Guardian* headline is highly dubious, but for the moment we simply note the deterministic framework within which the claims are being made.

One in twenty-five Americans now receive personalised genetic test reports that predict their probabilities of developing various medical conditions over their lifetime.[20] In 2017 alone, more people had genetic tests carried out than in all of the previous decade since they first became available. One might fondly imagine that when people are told that they have an increased probability of developing a certain disease, based on their genes, they will take extra precautions, such as a better diet and increased exercise, to avoid such an outcome. But surveys show that the opposite tends to be the case – once people learn that their chance of a disease, or a trait like overweight, is (supposedly) more based on genes than on the environment, they become more fatalistic (Dar-Nimrod et al., 2014, Persky et al., 2017). The genes seem to be more in control of the situation than they are. This presumably explains why many people experience more negative emotions and distress when informed about the higher genetic risk of developing a medical condition (Green et al., 2009, Bloss et al., 2011, Dar-Nimrod et al., 2013).

Statements on genetics in relation to the environment are generally made on DTC company websites in a reasonably judicious way. But occasionally claims are made with distinctly deterministic overtones. As the Map My Gene website assures us: 'Your DNA is the blueprint of life. It determines

everything from how you look to how you behave . . . . In MapMyGene, our goal is to unravel that secret to you.'[21] The DNA testing kit from the sequencing company 23andMe says 'Welcome to you.' The idea of a genetically determined destiny is reinforced by sperm banks that suggest that prospective users should consider the donor's educational record, his athletic prowess, hobbies and favourite foods, as if these were somehow written into the genetic script provided by the sperm. Human eggs can likewise be purchased online with accompanying details about the donors.

One of the problems with DTC genetic testing results is that the data can be passed on to third party app providers that then extrapolate even more wildly from the data than the original company that generated the data. For example, in 2019, a US entrepreneur called Joel Bellenson living in Kampala, Uganda, released an app that supposedly estimated a person's level of attraction to other people of the same sex (Maxmen, 2019). It is noteworthy that gay sex in Uganda is liable to lead to prison if the person is caught. According to Bellenson, he put together the app over a weekend based on the finding (discussed further in Chapter 10) that several variant genes correlate with those who experience same-sex attraction, despite the fact that the authors of the paper in question took pains to emphasise that a person's genes cannot predict their sexuality (Ganna et al., 2019). Bellenson posted his app on GenePlaza, an online marketplace for DNA interpretation tools, but after a few weeks of concerted opposition, GenePlaza removed the app. Up to 62 per cent of customers upload their genetic data on to third-party websites, seeking more interpretations of the data (Moscarello et al., 2019). The scope for misunderstanding the data is increasing, often leading to unnecessary scares and concerns for those who do so.

Particularly striking is the finding from a psychology research group at Stanford University that even telling people that they are more likely to develop a medical condition due to their genetic constitution causes people to display precisely the kind of risk factors for that condition (Turnwald et al., 2019). For example, merely receiving genetic risk information was enough to increase the heart rate, change how running perseverance was perceived during exercise and change how fullness was perceived after eating. So the genetic information changed the mindset of the people being studied in such a way that it increased the risk of developing precisely the syndromes for which they had been told they had a greater genetic risk. In fact, in some cases, the risk from being told was greater than the actual genetically predicted risk, so presumably in such cases it would be better not to tell people that they had an increased genetic risk at all! The situation is similar to the consequences of telling some people about the side-effects of

medications – when there is a greater prevalence of the side-effects compared with people who had not been told. We humans are highly suggestible.

Does all the outpouring of the language of DNA in popular culture and via the current enthusiasm for genetic testing contribute to the idea that we are really slaves to our genes? It's hard to say. But at the least it should act as a reminder of the way in which the language of science can be absorbed into public discourse and be deployed in ways that lie well beyond science. Given the long history of the ideological abuse of genetics, one cannot necessarily assume that such misuse of language is merely benign. Cultural osmosis is a powerful process in shaping attitudes, be they expressed in the context of politics, social attitudes, economics, sport or religion. It is only a century ago that we found Samuel J. Holmes, Professor of Zoology at the University of California at Berkeley, informing his readers in his book *Studies in Evolution and Eugenics* (1923) that anyone familiar with genetics could in a few generations 'breed a race of idiots, a race of dwarfs, a race of giants, an albino race, an insane race, a race of moral imbeciles ... a race of preeminent mental ability, or a race of unusual artistic talent'. There was no excuse, declared Holmes, to allow 'degenerate human beings' to reproduce (Paul, 1995).

Although the main aim of this book is to investigate the role of genetic diversity in differential human behaviours and whether, as a matter of fact, purported roles are validated by the available data, the considerable ideological investments often made in the outcomes of such assessments should act as a warning that in this branch of science more than others the scope for use and abuse remains particularly large. More examples illustrating this point will be given as different topics are addressed throughout the book, including intelligence testing, aggression, sexual orientation, religiosity and politics. The investigators who entitle their publication 'The Heritability of Foreign Policy Preferences' (Cranmer and Dawes, 2012) cannot seriously expect that their paper will be treated as 'pure science'.

Overall, therefore, 'genetic determinism' with all its various shades of meaning remains a lively topic in public discourse and the outcome of the discussion is not merely academic. Genetically deterministic beliefs often correlate with non-egalitarian attitudes and there is abundant evidence that beliefs concerning the fixity of human identity, be it for perceived genetic or environmental reasons, have a remarkably negative impact on human flourishing. Of course, the truth or falsity of beliefs does not hinge upon their consequences, even though those may be negative. However, given the history of ideological abuse of genetics, it is as well to be very sure about scientific claims and judicious in their public dissemination.