

# Genetics and identity; explaining our history, defining our futures?

**Barbara Jennings**

Genetics is a discipline that engages all of us. One of the first things that we do when we greet a new baby within a family is to compare their appearance and personality with those of his or her parents. We may also continue to take note of particular talents or perceived weaknesses throughout life, which we then connect with traits inherited from the parents or wider family. So, if we are defined by our genetics perhaps it is an instinctive human trait rather than something that science imposes on us. However, in this essay I explore the notion that a recent explosion in technology and genetic knowledge will help scientists to have a better understanding of both the history of human populations, and how medicine can be tailored to the needs of each individual. I reluctantly include some scientific jargon for precision, but identify these with italics and explain them in the glossary of terms below.

## The Human Genome Project

The completion of the Human *Genome* Project at the beginning of this century marked an important era for genetics. Policy makers showed almost as much interest in this achievement as scientists did; Bill Clinton claimed that “*genome* science will revolutionise the diagnosis, prevention and treatment of most, if not all, human diseases.” A few years after this radical statement, and 50 years after the discovery of the structure of DNA by James Watson and Francis Crick, the entire sequence of the human genome was determined<sup>1</sup>.

The goal of the Human *Genome* Project was to produce a single continuous sequence for each of the 24 human *chromosomes* and to define the order of all of the *genes* on these large *DNA* molecules. Each of our *genes* can be

<sup>1</sup> [http://www.ornl.gov/sci/techresources/Human\\_Genome/home.shtml](http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml)

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*Opposite:*  
This image of the DNA double helix, made from hundreds of different faces, appeared on the cover of the journal that announced the sequencing of the human genome. *Nature* 409; 2001. Illustration by Eric Lander, created by Runaway Technology Inc. ([www.photomosaic.com](http://www.photomosaic.com)) using Photomosaic by Robert Silvers from original artwork by Darryl Leja. Used courtesy of the Whitehead Institute for Biomedical Research.

**The original short letter to Nature that first described the structure of DNA.**  
(Watson J.D. & Crick F.H.C. (1953) *A Structure for Deoxyribose Nucleic Acid.* *Nature* 171, 737-738)

### MOLECULAR STRUCTURE OF NUCLEIC ACIDS

#### A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey<sup>1</sup>. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagram is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxy-ribofuranose residues with 3',5' linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There

The figure is merely diagrammatic. The ribbons symbolize the phosphate-sugar chains, and the horizontal lines the pairs of bases holding the chains together. The vertical line marks the fibre axis.

is a residue on each chain every 3.4 Å, in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 Å. The distance of a phosphate atom from the fibre axis is 10 Å. As the phosphates are on the outside, cations have easy access to them. The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact. The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases

are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally<sup>2,3</sup> that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

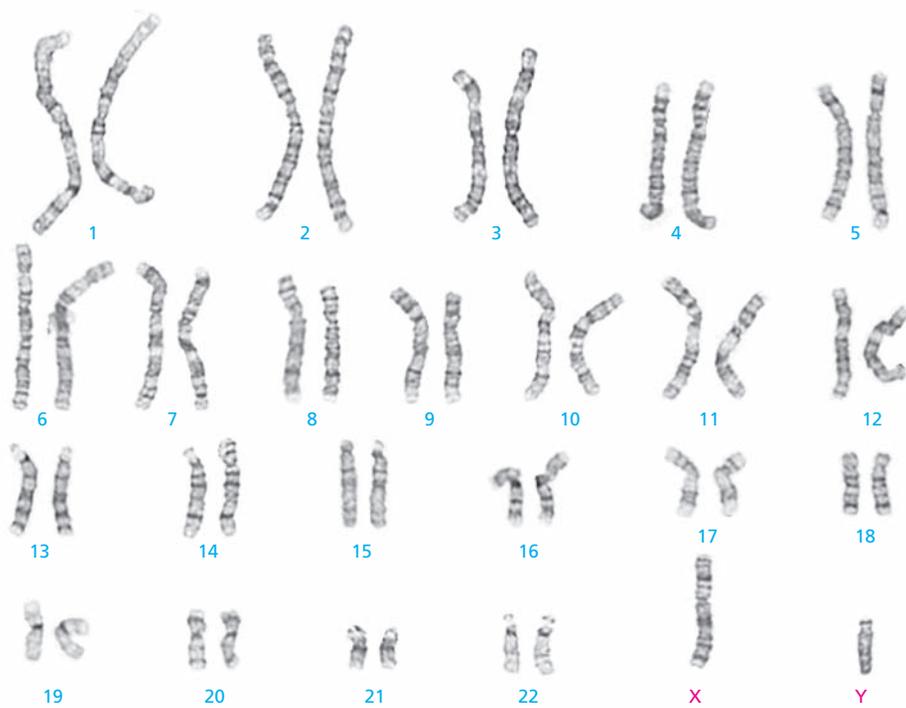
The previously published X-ray data<sup>4,5</sup> on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of those are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material. Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on inter-atomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at King's College, London. One of us (J. D. W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

J. D. WATSON  
F. H. C. CRICK  
Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems, Cavendish Laboratory, Cambridge, April 2.

<sup>1</sup> Pauling, L., and Corey, R. B. *Nature*, 171, 346 (1953); *Proc. U.S. Nat. Acad. Sci.*, 38, 81 (1952).  
<sup>2</sup> Furberg, S. *Acta Chem. Scand.*, 6, 634 (1952).  
<sup>3</sup> Chargaff, E., for references see Zamboni, S., Braverman, G., and Chargaff, E., *Biochim. et Biophys. Acta*, 8, 62 (1953).  
<sup>4</sup> Wyatt, G. R., *J. Gen. Physiol.*, 26, 201 (1952).  
<sup>5</sup> Chargaff, E., *Ann. N.Y. Acad. Sci.*, 58, 211 (1952).  
<sup>6</sup> Wilkins, M. H. F., and Randall, J. T., *Biochim. et Biophys. Acta*, 10, 192 (1953).

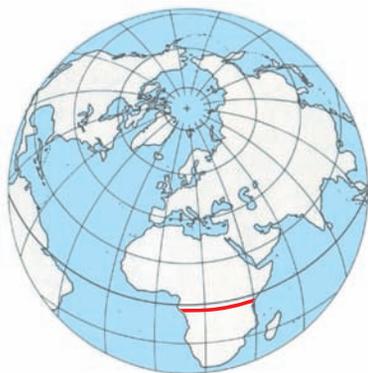


**The chromosomes of a normal human male.** All human cells contain 22 pairs of chromosomes, one set from the mother and one set from the father. In addition females contain two copies of the X chromosome, one from the mother and one from the father. Males contain one X chromosome (from the mother) and one Y chromosome (from the father). Whereas the X chromosome contains more than 1000 genes, the Y chromosome only contains about 80, but it is the presence of the Y chromosome that determines the sex of the individual. Those without a Y chromosome develop as females; those with a Y chromosome develop as males. (Courtesy of Julie Robertson of the Wisconsin State Laboratory of Hygiene.)

**DNA and the human genome.** (A) In this image we see the classical DNA double helix. Each pair of the DNA building blocks, called nucleotides, are magnified to span 1 millimetre and we see just 40 of them here. However, there are approximately 30 billion of them in the human genome. (B) Using this same scale the entire human genome would extend 3200 kilometres, which is far enough to stretch across the centre of Africa, the site of our human origins. (from Alberts B. et al Essential Cell Biology 3rd Edition, Garland Science, 2010)



(A)

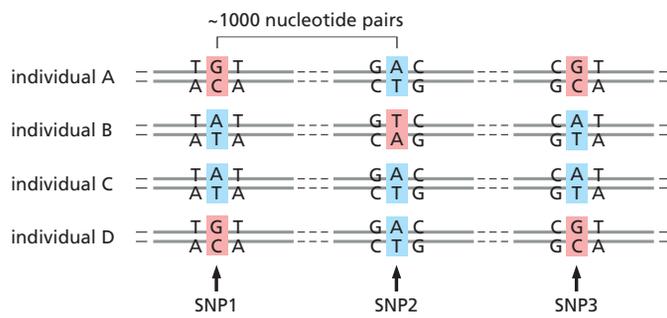


(B)

seen either as a blueprint for our individual traits, or as a code for each individual protein produced by the cells of our bodies or even as a vulnerable code that can become corrupted or mutated, sometimes leading to disease. However they are viewed, *gene* sequences are important and interesting. In 2003 the finished version of the human *genome* sequence was in place, this was two years ahead of schedule and under-budget; a pretty remarkable achievement for what was largely a publicly funded project that depended on international collaboration.

The meaning of the term *genome* depends on its context, but the nuclear genome of most human cells consists of two sets of 23 *chromosomes*; each set containing more than 3 billion base pairs of *DNA*. Of this vast sequence, less than 2% is what we call coding *DNA*, defining the proteins that our bodies need. Through the Human *Genome* Project we have discovered that there are less than 24000 coding *genes* in humans, only twice the number that a worm or a fruit fly has. This finding was a surprise to the *gene* hunters, and further encouraged scientists to think about interactions between *genes*, and between *genes* and environments to understand complex biological problems such as the cause of common human diseases.

The first phase of the Human *Genome* Project was about finding consensus by producing a map derived from sequencing several individual



**Single-Nucleotide Polymorphisms (SNPs)** are sequences in the DNA of the human genome that differ by a single nucleotide pair between one portion of the population and another. Most such variations, which occur roughly every 1,000 nucleotides along the DNA, are located in regions of the genome where they do not significantly affect the function of a gene. (from Alberts B. et al Essential Cell Biology 3rd Edition, Garland Science, 2010)

genomes and looking for the sequences that defined or united all human beings. We now estimate that all people are 99.9% identical; genomes from unrelated individuals only differ on average every 1000 base pairs. But it is the nature of this variation that is the new focus for the gene sequencers and mappers.

When we observe people we see enormous diversity in appearance, personality and health; some of this diversity can be explained by the 0.1 % of DNA sequence difference found between individuals. The DNA sequence is constructed from four different bases, abbreviated to the four letters A, T, G and C. Much of human variation is caused by single base differences between sequences; so a chromosome site with base A in one individual may have G in another individual. These variants are known as *single nucleotide polymorphisms (SNPs)*. About 30 million SNPs have been estimated to exist in human genomes and there is a massive international effort in place to discover the common clusters of SNPs that are usually inherited together (*haplotypes*) in several ethnically diverse populations. This is known as the HapMap project<sup>2</sup> and its aim is to generate data that will give geneticists a much-needed short cut in their search through many millions of SNPs for those linked to a human disease.

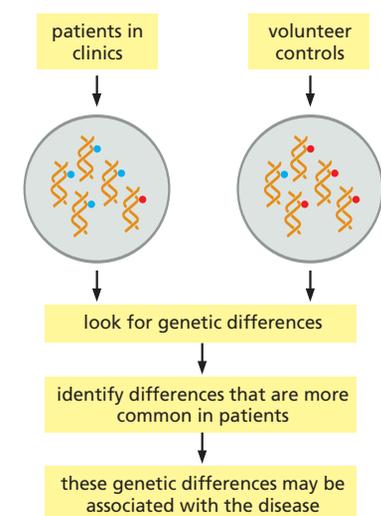
### Ancestry

Our ethnicity and where we imagine our ancestors came from seem to matter a great deal in constructing our fragile identities. Those engaged in genealogy may uncover a particularly harrowing chapter of an ancestor's life-story and be deeply moved by it, even when that person lived several generations ago. This fascination with our heritage can certainly span the centuries and even the millennia, with an interest in the migrations across continents that led to the establishment of our communities and cultures.

Common *haplotypes* occur in all populations worldwide; but their frequencies vary between ethnic groups, for example some are more common in populations of western European origin while others are more common in populations of Han Chinese descent. So the frequencies of genetic variants tell some of the story of human history. Our genetic

<sup>2</sup> <http://www.hapmap.org/>

**Genetic Disease Association Studies.** The DNA of patients from disease clinics is compared with a healthy volunteer control group. If some DNA variation, for example a group of SNPs, is more common in the patients (as indicated by the blue squares) than in the control group, then it is associated with and may be an important marker for the disease. In these experiments, it is important that patients and volunteer controls have the same ancestry. (courtesy of People of the British Isles Study, Oxford University)



legacy can certainly be traced, not only in the *DNA* of our families but also in the populations that we are descended from. Genealogy used to rely on historical records but increasingly involves *DNA* testing to trace our maternal or paternal lineages or even whole genome analysis, employing *ancestry informative markers*. As I write this, in early 2009, many commercial labs offer such *DNA* testing services to tell you about your ethnic heritage. To date, the genetic science community remains pretty sceptical about how informative such expensive tests truly are but several large studies are generating data about the genetics of populations that will refine this area of science over the next few years.

One such study in the U.K. is funded by the Wellcome Trust and headed by the geneticist Walter Bodmer and his lead scientist, Bruce Winney at Oxford University. The *People of the British Isles Project* has recruited volunteers whose grandparents all came from the same rural area in populations selected across the U.K.; from the Scottish Isles in the north west to Norfolk and Suffolk in the east<sup>3</sup>. Blood samples have been collected from nearly 4000 individuals and their *DNA* is now being subjected to thousands of tests for SNPs. The data and samples generated in this project will be important in two main ways. First, they will be used by medical scientists who are looking for significant genetic markers of disease risk and variants that will predict drug response; this type of genetic medicine is discussed in more detail below. Second, this snapshot of the U.K. population will tell us how mixed up our community is genetically or perhaps how stratified it is, because the volunteers from these rural populations may have distinct genetic profiles that clearly reflect their historical lineages. The results that are generated may help to resolve a central question about the historical origin of the British that still taxes modern historians because there are two conflicting theories about our heritage. The first is that waves of invasion, military conquest and power transfer from Ancient Briton to Roman to Anglo Saxon have shaped the British gene pool. The more modern perspective is that culture and skills were introduced and assimilated from other European populations with little alteration to the gene pool; so much of the population will have a similar genetic heritage to the hunter-gatherer ancestors who came to the British Isles after the last ice age. This idea of "acculturation" rather than conquest is discussed in Robin McKie's book, *Face of Britain*<sup>4</sup>. McKie also presents the existing genetic evidence for the two theories and explains why the *People of the British Isles* study may resolve the dispute. Previous attempts to address the question with *DNA* evidence generated conflicting conclusions but Bodmer's study has two significant advantages for tackling the problem. First, the cohort being examined is large and is being studied with thousands of genetic markers and secondly, volunteers probably represent a geographically stable population from the early twentieth century because all four of their grand-parents were born in the same rural district. An early illustrative experiment from Bodmer's study considered rare genetic variants of the gene, called *MC1R*, which is

<sup>3</sup> <http://www.peopleofthebritishisles.org/>

<sup>4</sup> Robin McKie, *Face of Britain*, Simon and Shuster, 2006.

associated with red hair. These rare variants were found to be more common in the western U.K. areas associated with Ancient Briton settlements, sometimes referred to as the Celtic Fringe, than in the east of England where there were Anglo-Saxon settlements suggesting that *clines*, or gradients of prevalence, do exist for particular traits in the British *gene* pool.

We have a seemingly insatiable appetite for understanding the history of, and relationships between, human populations using archaeology, written documentation and technologies such as molecular genetics. We even put huge effort into understanding the genetics of our close relatives, the Neanderthals, whose remains are being analysed in their own *genome* project<sup>5</sup>. We know from such studies that Neanderthal and modern human populations shared a European history tens of thousands of years ago. This raised the possibility that interbreeding could have occurred between the two species. However, through the *genome* project work of a team headed by Svante Pääbo we know that there is still no DNA evidence for this hypothesis despite a painstaking search.

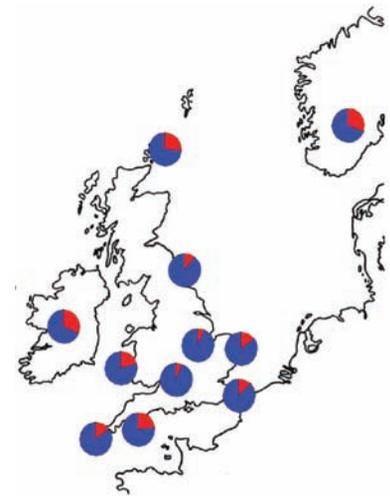
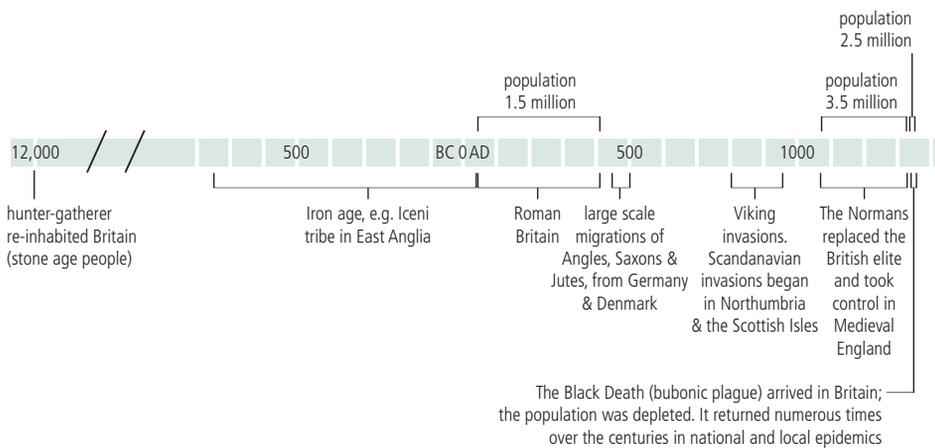
### Genetic Medicine

In the twentieth century the use of genetics in medicine was mainly focused on rare diseases that clearly ran in families such as cystic fibrosis, muscular dystrophies and haemophilias. These are referred to as *single gene disorders* or *Mendelian traits* because those individuals with copies of the rare causative *mutations* would develop the disease according to inheritance patterns that were first described by Gregor Mendel in the nineteenth century.

This century, genetic science is touching many other areas of medicine as it is realised that most common diseases have a genetic component; though not everyone with these particular genetic components will go on to develop the disease.

As our understanding increases it is expected that a new area of genetic medicine will arise, this is most often referred to as 'personalised

<sup>5</sup> <http://www.eva.mpg.de/neandertal/>



**Genes and Red Hair.** Shown here is the distribution of two different variants of the gene *MC1R* across Britain. Each circle shows how common the variants are in each region of the country looked at so far. The proportion of the circle in red indicates how common the red hair-associated variants of the gene are in that region. The Celtic Fringe regions (associated with Ancient Britons) appear to have a higher frequency of the red hair-associated variant of the gene than 'Anglo-Saxon' England in the east.

(courtesy of People of the British Isles Study, Oxford University)

**Timeline of some of the events that shaped the population of Britain since the end of the last ice age, about 12,000 years ago.** Britain has been occupied by modern humans (*Homo sapiens*) for tens of thousands of years but the biological ancestors of many twenty-first century British people arrived just after the last ice-age.

medicine'. There are two potential applications in this field. First, those with genetic predispositions to conditions such as cancer, dementia and heart disease could be identified and offered a subsequent management plan aiming to prevent or delay the onset of the disease. And second, the use of genetic testing to predict people's response to commonly prescribed drugs, this is known as pharmacogenetics. So genetics in medicine is set to become the concern of most medical practitioners over the next decade and will be an area of increasing interest to all of us.

### Examples of genetic disease

Rare single gene disorder with high penetrance	Rare family cancer syndromes with incomplete penetrance	single gene disorders with low penetrance	Polygenic traits	Pharmacogenetic trait
Huntingdon's disease, (penetrance ~ 100%) Haemophilia	Hereditary non-polyposis colorectal cancer (penetrance ~ 80%)	Hereditary haemochromatosis. Estimates for clinical penetrance vary from 20% to >1%.	Type 2 diabetes Asthma Schizophrenia. Caused by the additive effect of multiple genetic and environmental factors. Penetrance is very low for each individual variant.	Poor metaboliser of anti-depressants and anti-psychotics - leads to abnormal movements and other adverse effects. Variants of interest are very common in the population.

### Good genes, bad genes and risk management

Some relatively common SNPs seem to define a tendency to get serious disease. A variant of one *gene*, *HFE*, can lead to a life-threatening disease called hereditary haemochromatosis in individuals who have inherited that variant from both parents. Individuals with this double dose of a particular genetic variant are referred to as *homozygotes*. Undiagnosed hereditary haemochromatosis causes a host of medical problems in later life, from diabetes and arthritis through to liver cirrhosis and liver cancer. However, there is a simple and effective treatment for the condition if it is diagnosed early and this involves a sort of controlled blood letting. The disease is characterised by an over-load of iron in the body, because the *HFE* variant disrupts the normal controls that the gut has for absorbing just the right amount of iron from our diets. Removing blood from the patient, in a session that is similar to a blood donation clinic, will simply reduce large iron stores that could otherwise damage essential organs. The need for early treatment was a rationale for developing a diagnostic genetic test for symptomatic individuals and their families. This test is used routinely in most U.K. hospitals.

The *HFE mutation* that underlies hereditary haemochromatosis is the most common disease-causing variant in populations of northern European origin. Its prevalence has been associated with populations that were founded by Viking ancestors. It is interesting to speculate about why a *mutation* that is potentially so life-threatening should be so common in some populations. Why, from an evolutionary perspective, has it been such a successful genetic variant? There are many ideas about this, mostly to do with the advantages of storing iron, a mineral that is essential for life, in times of deficiency. The point is that this apparently 'bad' genetic variant

must have proven to be a 'good' trait at some point in the history of human populations.

One era to consider is the 14th century when *Yersinia pestis*, a bacterium responsible for the bubonic plague, was wiping out a significant proportion of Europeans. But the bacterium did not infect everyone and nor did it prove fatal to all those who were infected. Undoubtedly many factors, both genetic and environmental, will have influenced who lived or died. But it is possible that the abnormal physiology found in those with *HFE mutations* actually helps combat bacterial infections. Because while iron is stored in excess in many tissues of the body of the haemochromatosis patient, it is actually in very short supply in front line cells of the immune system known as macrophages; and bacteria often use the iron from these cells to grow and divide. So perhaps folk with haemochromatosis have an advantage in that the relatively low iron in their macrophages discourages bacterial growth and so infections do not persist? If this is correct, perhaps *HFE mutation* carriers had a greater chance of surviving the plague, were able to have children and pass on this *mutation* to new generations, and then homozygous individuals were in late middle age before experiencing the fatal consequences of their genetic heritage<sup>6</sup>.

A second paradox relates to how common the *HFE* mutation is; about 1 in 200 of the Norfolk population have the at-risk genetic profile for developing hereditary haemochromatosis but less than 1 in 10,000 individuals are actually diagnosed with the disease<sup>7</sup>. The degree that a given genetic fault manifests itself in an individual is referred to as *penetrance*, and the low *penetrance* of many common, disease-associated *mutations* means that there is little value in population screening programmes despite the routine availability of the genetic testing technology.

A gradient of prevalence is seen for the distribution of *HFE* mutations across Europe, with high prevalence in the north and lower prevalence in southern Europe.

The converse picture is seen for a variant of the *gene MTHFR* which is thought to have a role in cardiovascular disease; the prevalence of one *mutation* being highest in populations of Hispanic origin and lower in northern Europeans. That variant has been associated with an increased risk of diseases such as stroke, myocardial infarction and deep vein thrombosis. These conditions are seriously big killers at a population level

<sup>6</sup> These ideas are explored by Sharon Moalem in *Survival of the Sickest*, Harper Collins, 2007.

<sup>7</sup> We published some of the first evidence for the low penetrance of the *HFE* gene mutations in 1997/9.

Willis G. et al. *Haemochromatosis gene mutation in hepatocellular cancer*. *The Lancet*, 1997, 350:565-6

*Haemochromatosis gene C282Y homozygotes in an elderly male population*  
*The Lancet*, 1999, 354: 221-222

so even if the genetic risk factor makes a very small individual contribution to disease susceptibility, it could still play a significant role in overall disease burden. However, as with *HFE mutations*, there may be selective advantages for the apparently harmful form. In fact studies have shown that it may be protective against colorectal cancer and that dietary modifications such as taking the B vitamin, folate, can prevent the cardiovascular consequences of this *mutation*. Furthermore, there is evidence that when dietary folate levels are adequate in a pregnant woman that foetuses with this variant have a selective advantage<sup>8</sup>. So a factor that aids survival in the womb may be one that presents significant health risks in late middle age and beyond; but these risks could be modified through dietary interventions.

Common genetic variants are considered to be potential screening tools. In the future it is possible that we will each have our own programmes for detecting early signs of cancer, heart disease and dementia based on our genetic profiles. This could be coupled with an individualised diet and lifestyle schedule to form a disease prevention strategy. The advantage of a personalised approach that has to take account of the complexity described above, over the use of public health strategies aimed at whole populations, remains controversial.

One area of concern is that information that predicts future bad health could be strongly stigmatising, both for the individual's own sense of identity and how they are viewed by society.

### Pharmacogenetics

An area of genetic medicine that is much more likely to expand over the next decade is pharmacogenetics. This term describes the development and application of *DNA*-based tests that will tell us how much of a particular medicine should be prescribed for each individual.

We know that a 'one size fits all' dose is not appropriate for many commonly prescribed drugs. This is because genetic variations affect both how rapidly a drug is cleared from our bodies and also how much drug is required in the first place to saturate its target. Some individuals who are rapid metabolizers of commonly prescribed medicines gain no benefit from their treatment, whilst others can suffer life-threatening side effects because they are such slow metabolizers.

For some medicines, these scenarios are well characterised at the molecular level. Isoniazid is a drug used in the treatment of tuberculosis, for example. The rate of isoniazid metabolism is genetically determined and there are known variants that lead to rapid metabolism and other variants that lead to slow metabolism with the accumulation of drug in the patient with severely adverse consequences, these include

<sup>8</sup> Lucock M et al. *A critical role for B-vitamin nutrition in human developmental and evolutionary biology*. *Nutrition research* 2003, 23:1463 -1475.

neurotoxicity and anaemias. Another example involves a form of chemotherapy, 5-fluorouracil, used in the management of many common cancers, including colorectal cancer and this drug targets an enzyme pathway that is highly variable between individuals. One of the challenges of using chemotherapy is that the therapeutic dose is very close to the dose that is life-threatening because normal cells are hit by the drug alongside the cancer cells; and so pharmacogenetic approaches to find the optimal dose for an individual could be particularly beneficial. There are many studies underway to identify all of the common genetic variants that affect the use of chemotherapy in cancer patients.

A crude form of pharmacogenetics is already applied in medicine because we know that certain genetic variants involved in drug metabolism are more prevalent in populations from some parts of the world than others. For example, the slow Isoniazid metabolisers are often found in Middle Eastern populations but rarely in Japanese populations. There is a danger that certain drugs are abandoned because of common side effects for some populations but it strikes me as quite odd that modern healthcare systems apply this blunt epidemiological instrument rather than a much more specific *DNA* based test. Particularly because projects like HapMap show that there is much more genetic variability within different ethnic groups than between them.

If we compare genetic tests for variants that affect drug metabolism with those that affect disease susceptibility there are reasons why the former are likely to be used more widely in modern medicine. First, most individuals with a pharmacogenetic variant will go through their entire lives without the genetic trait becoming apparent as they are unlikely to be exposed to the particular medication. For this reason and because the tests relate to modern medicine only, these variants have not been selected against and so are relatively common traits, they may also be traits with relatively extreme phenotypes. Secondly, because the tests are specific for a particular medication only there are rarely implications for other family members or indeed any social consequences for the treated individual from taking a particular genetic test, such as insurance or employment discrimination based on genetics.

### **Nature AND Nurture: Am I My DNA?**

Because genes are perceived to be unchanging (despite mutations occurring with every cell division, the vast majority of one's *genome* is pretty much fixed for life) and easy to analyse with today's technologies, the deterministic view is that using genetic analysis could be like looking into a crystal ball, not just for oneself but for one's siblings and children too. Such a view could lead to genetic discrimination.

However, our environments are huge modifiers of our genetic legacy and an apparently bad form of a gene in one environment is very beneficial in a different environment or at a different point in our lives. Also, *genes* are not just blue-prints, their products actually orchestrate and respond to the



courtesy of Wellcome Images

activity of other *genes* and to everyday physiological processes from digestion and breathing, to thinking. Even individual experiences will alter the activities of your *genes* and such potential diversity of outcome makes determinism seem implausible as well as undesirable.

## Glossary of Terms

**Ancestry Informative Markers (AIM);** are sets of markers of genetic variation that show substantial different frequencies between populations depending on their geography and/or ethnic origin.

**Base;** A chemical group found in the DNA building blocks. The DNA sequence comprises a four letter code of bases A, T, G and C.

**Cline;** A gradient or gradual change in gene frequency or phenotype over a given geographical area

**DNA;** the abbreviation for the large molecule, deoxyribonucleic acid. This is the genetic material that our genes are comprised of.

**Gene;** An inherited factor that determines a specific observable trait (biological function or physical feature).

**Genome;** a complete set of 23 *chromosomes* inherited from one parent. The human genome contains almost 24,000 genes.

**Chromosome;** Very large macromolecule comprised of DNA and protein, each chromosome contains a linear arrangement of genes. There are 24 human chromosomes; numbers 1 to 22 and the sex chromosomes, X, and Y.

**Haplotype;** A set of linked genetic variants found in a region of a chromosome. These variants are linked because they are close together on the same strand of DNA and therefore tend to be inherited together from one generation to the next.

**Heterozygote;** An individual with two different gene variants inherited from their maternal and paternal lines.

**HFE;** the code name for the gene that is usually mutated in patients with the iron-overload disease hereditary haemochromatosis

**Mendelian trait;** A condition caused by one mutation or two mutations being inherited for a particular gene

sequence. The characteristics or phenotypes for these mutations occur, on average, in fixed proportions according to rules or laws first described by Gregor Mendel after his famous studies of garden peas.

**MC1R;** the code name for the gene that has a role in skin and hair pigmentation. Two rare variants of this gene called 150C and 161W are associated with red hair.

**MTHFR;** the code name for a gene that encodes a protein that is involved in the biochemical pathway that metabolises the nutrient folate and which metabolises homocysteine.

**Mutation;** A change or variation in the DNA sequence at a given chromosome location or gene sequence. The term is used to describe both the process of change and the variant itself. Every time a cell divides, and every time an egg or sperm is produced, DNA is copied. Despite proof-reading and error correcting machinery in our cells, mistakes still occur and are passed from generation to generation of cell or individual. These mistakes or changes are mutations. The terms mutation, variant and polymorphism are used interchangeably throughout the essay but to be precise, a polymorphism usually describes a common variant that is found on more than 1% of chromosomes.

**Penetrance;** The percentage of individuals who demonstrate a particular trait or phenotype that is expected to arise from a given genetic variant or mutation. For some *single gene disorders* such as Huntington's disease, the mutation will have 100% penetrance. For most common diseases, the penetrance of a particular mutation is very low and the phenotype will depend on other genetic and environmental factors.

**Single gene disorder;** A condition caused by one mutation or two mutations being inherited for a particular gene sequence (see *Mendelian trait*).

**Single nucleotide polymorphism or SNP;** A site in the genome where the DNA sequences of many individuals vary by a single base.