THE SCIENCE OF ONE LIFE AT A TIME[1]

ROBERT POLLACK

749 Fairchild Center, Mail Code: 2419, Columbia University
New York, NY 10027, USA

> "Nothing that is worth doing is completed in our lifetime, therefore we must be saved by hope. Nothing true or beautiful or good makes complete sense in any immediate context of history; therefore we must be saved by faith. Nothing we do, however virtuous, can be accomplished alone; therefore we are saved by love."
> Reinhold Niebuhr, "The Irony of American History"

ABSTRACT

Genetic medicine is the branch of science that depends on a knowledge of many lifetimes, much history, and vast collaboration. The trick will be to see that it is informed, as Niebuhr would have it, by hope, faith and love. Certain current practices in genetic medicine do not promise much of any of these three, all of them being the irrational properties of a religion. I will consider ways that hope, faith and love might be returned to genetic medicine, that part of medical practice invested in a future of ever-expanding genetic knowledge. Without our choice to act now to return to these, every person will one day be obliged to pay attention to genomic news in a context possibly not devoid of faith or love, but certainly devoid of hope. There already are a few people who have had to deal with genetic news in this gloomy context. These are the descendants of genetic bottlenecks, members of groups of people – apparently unrelated – who share a small number of common ancestors. The Jews of Eastern Europe – the Ashkenazim – are one of these groups. How Jews and others respond to this challenge should be of interest to everyone whose recent family history includes the inheritance of unusual versions of one or more genes; that is, everyone.

INTRODUCTION

It is hard to live in two worlds. I would like to be able to say that every day I choose by my own free will to live my life according to the laws of my religion, but the truth is I do not. Instead I often find myself choosing reason over irrational obligation, and cutting the corners of my religious obligations to myself and others. I would like to say, as well, that every day I find the strength to reopen my own examination of the natural world, through my eyes or the eyes of my scientific colleagues, ready to accept the implications of these discoveries no matter how hard they may be to fit into the rules by which I choose to live. But here too I often fall short, walling myself off from these implications in order to focus on the beautiful, elegant details of nature.

There are days when both traditions cooperate, and the workings of nature fit well enough with what for the moment I sense are an unknowable God's intentions, that I can both understand an aspect of the world's design and feel its purpose, and the meaning it gives to my place in the world, at the same time. On the other days – most days — I feel I must pick between data and feeling. That is just the choice genetic medicine seems to face today. In both cases, this choice is no choice at all: for my state of mind and for genetic medicine's current practices, the denial of feelings for the sake of the data is not a moral option. The real choice made available by free will is always to work with both the feeling and the data, or with neither. On my bad days, as in many of genetic medicine's current practices, the choice is not to use one or the other, but to use neither.

The better choice for medicine, as for me, is always to use both. The most important field in medicine for this choice to be made more widely available, right away, is the field of medical diagnosis informed by human genetics. There, the tools of science offer the opportunity to obtain data which a proper regard for feelings would oblige us to leave in darkness. Brought to light in the wrong context, these data must cause a vast amount of bad feeling and unnecessary emotional pain. There are many examples to choose from in describing this situation. I will discuss in detail one I am most intimately familiar with: the genetic markers – the specific DNA sequences found in the genomes – of some but not all Jews.

HUMAN DIVERSITY WITH GENETIC CERTAINTY?

---

[1] From ***The Faith of Biology and the Biology of Faith: Order, Meaning, and Free Will in Modern Medical Science***, Robert E. Pollack, Columbia University Press, 2000.

The importance of each person's individual choices is central to the Jewish tradition, but it is nevertheless easy enough to lose sight of free will in the details of obligatory observance. The worst mistake one can make in this regard is to think one has understood the meaning of a ritual when one in fact has missed the point completely. A little more than a year ago, for example, I received a notice by email telling me of a departmental faculty meeting that would fall on the first day of the Jewish new year, Rosh Hashanah. I sent back an email saying no, I'd be celebrating the 5,758th anniversary of the creation of the universe that day, and could not be at the meeting.

My absence annoyed many members of my department; some who were Jewish thought I was kidding, others who were not thought I was just nuts. I thought I had acted honestly, freeing myself for this celebration of creation. I had forgotten that the day has other names: "Yom HaZikharon," or Memorial Day; and "Yom HaDin," the Day of Judgement.

Afterward, when I told Rabbi Adin Steinsaltz of my colleagues' response, he asked: could my department perhaps have been trying to teach me? Were my colleagues perhaps annoyed at me not for my piety, but for my ignorance? Rosh Hashanah, the first day of the Jewish year, is not the anniversary of the creation of the world. It is the anniversary of creation's sixth day, the hours of the appearance of our common human ancestors, their short stay in Eden, and their exile into a world where their further actions – freely chosen – would have consequences.

The ancient Jewish recognition of a shared ancestry of all people produces a second, equally unquestioning presumption, one that emerges from the idea of a Day of Judgement: that the immeasurable, infinite value of each human life derives not from any aspiration to perfection, but precisely from the inherited differences that allow each of us to look different, and to choose differently, from all others.

The earliest part of the Talmud – the Mishnah – is a record of expectations and laws binding on Jews, codified almost two millennia ago. When I first began to speak on the utility of my own tradition to my science some years ago, Professor David Weiss-Halivny gave me a reference in Mishnah Sanhedrin which has a commentary on the book of Genesis that makes this point with special elegance. The Mishnah is giving the reasons why witnesses to capital crimes must be taught that a person's life is at stake in their testimony, and that any person's life is a more serious matter than most anything else. The Mishnah then comments:

> "...for this reason one individual Human Being was created...to proclaim the greatness of the Holy One the Blessed: for a man strikes many coins from one mold and they all resemble one another, but the supreme King of Kings, the Holy One the Blessed, stamped every human in the stamp of the first human being and yet not one of them is like the other. Therefore every person is obliged to say: the world was created for my sake."

What remains today of the certainty that "and yet not one of them is like the other?" At the deepest level of the letters in our DNA genomes, it is indeed the case that "not one is like the other." Except for twins and other children who emerge from the same single fertilization of an egg by a sperm, any two people in this audience will have genomes three billion letters long that differ by about one letter in every few hundred.

Because the genome is so wonderfully long, even siblings have genomes that differ in millions of places. Genetic variation among parents and the iron rule of sexual reproduction — that in the production of sperm or egg a choice will be made for every gene, with one version being discarded and one version passed on to the next generation – guarantee that while children of the same parents may resemble each other, they will not be identical unless they come from the same fertilized egg.

This raises an interesting question: if we are all so different from one another, why do siblings resemble each other more than any two people chosen at random? Brothers and sisters – and even cousins, who share grandparents rather than parents — look similar even though each is genetically distinct from the others, because their only genetic differences are taken from a very small number of choices, the particular versions of any given gene carried in their parents' genomes.

Even a three-generation family is genetically restricted by the versions of genes available from common grandparents, although the restriction is moderated for cousins by the genetic choices provided to each through a different second set of grandparents. That is why the resemblance among cousins is usually less striking than among siblings, but far greater than among two randomly-chosen people. The broad generalization that people look more different from one another the less they are related by recent common ancestry, also tells us that the human species has been, over most of its history, quite happy to make babies with strangers.

If our species' history was instead one of widespread inbreeding or endogamy – the selection of a mate from one's own extended family rather than from a strange one – then we would expect that over time different extended families – and therefore sets of parents within those extended families - would each carry the badge of their history as a set of shared versions of the human genome. The data we have tell us instead that over the past few dozens of centuries since the last ice age, human genomes have been constantly sifted and resifted in the making of babies, with very little in the way of ancestral fastidiousness beyond the grandparental level to reduce the genetic variation from one extended family to another.

Each of us is a member of a very recent family that shares only a tiny fraction of the total human genetic diversity available. We are nevertheless all members of one family in the deep historic sense that our species has interbred widely for most of its history; that is why there are no

versions of a gene that are present only in one place on the planet, and none that are wholly absent from any reasonably large population, no matter how isolated.

In between the nuclear family of the greeting card and the global family of the Mishnah, there are a host of other, less recognized subpopulations or "families" of various sizes, each made up of people sharing the genetic choices of their distant common ancestors. Genetic diseases are sometimes said to run in families. Which families do we mean? In fact inheritance of the propensity to develop a disease can occur in all three sorts of families.

FAMILIES AND DISEASES

Versions of genes associated with a disease may have survived in a family or a sub-population for many reasons. Some may be here as the result of natural selection, good examples of the cold difference between its power to select for a difference that aids the survival of a species, and its complete disinterest in any one individual's fate. One could imagine the utility to a species that is always hungry, of any version of a gene that left an individual alive and well long enough to make many babies, and then – by speeding mortality – removed him or her from the pool of superfluous persons still needing to be fed.

Other non-functional versions of a gene might be present in a population because natural selection has had no grip on them, or because the variant that causes a disease in modern times might have been one that conferred a survival advantage in earlier, less hygienic times. For instance, well-fed, overweight people descended from the survivors of many generations of near-starvation often show a "thrifty" metabolism, a survival-response to caloric restriction that makes weight-loss difficult. Natural selection is wonderfully obtuse, and what might have been necessary for survival under one set of circumstances can easily become a burden under another.

The life expectancy of the human species in the absence of sufficient food, clean water, and separate sewage disposal is about half of what it is in the presence of such nineteenth-century medical advances. As life expectancy increases for more of the human population, we are bound to discover more such versions of genes in our midst. Any versions of a gene that might have helped to survive starvation, parasites, or fecal contamination of food and water would have been strongly selective until only a short time ago. If they also led to death in the fifth decade or later, no one would have even known about that until very recently.

Although the evidence for past utility must remain circumstantial, we have some good examples of this. Mutations in red-blood cell hemoglobin that may cause sickle-cell anemia or Thalassemia are with us today because they offer strong survival value in the presence of malaria, and mutations in CFTR which can cause cystic fibrosis at one extreme may well be with us today because they mitigated the lethal consequences of cholera in the past.

Two historical explanations of a late-onset inherited disease – the random noise of neutral mutation or the palimpsest of earlier advantage – fit well into the medical agenda that gives medical meaning to more immediate genetic conditions: isolate the gene, understand how it works in the normal case, and provide treatments to ameliorate its mutational disability. But there is a third historical explanation for the persistence of a genetic malady in a sub-population, one that produces circumstances for doctor and patient alike which open the risk of a breach in the capacity of medicine to confer a moral meaning on DNA-based data.

That breach occurs when the reason for inheritance of the condition is not drawn from the deep past, nor from recent family history, but from the midrange. In those cases, having inherited a gene associated with a disease may be the consequence of the history of nations, and DNA-based diagnosis of it will not easily be extricated from its political and religious implications.

Consider the cheetah: as a species in the wild it has been threatened for centuries, its coat much sought-after, its habitats encroached upon, its behavior poorly compatible with human society. Almost obliterated more than once in the past, all cheetahs today are the descendants of a very few ancient cheetah families. As a result, today's cheetahs – apparently unrelated, certainly not able to mate with each other when they are raised in separate zoos – are nevertheless all far more alike in appearance than any two randomly-picked lions, or tigers. Their DNA tells why.

For any given cheetah gene there is a very good chance that any two cheetahs share the same version, because all but a very few versions of any gene were lost when all but a very few ancestors were killed in past encounters with our species. Cheetahs are not quite clones of one another, but they are as alike – or more so – than a set of children in one large family. Survivors of a genetic bottleneck, cheetahs that appear to be unrelated have DNA that tells us they are survivors of a past disaster, the genetic constriction called a founder-effect.

A high probability of inheriting precisely the sort of version of a gene that no one wishes, can be the result of having an unexpected founder-effect in one's past family history. The founding members of such a family would have to have survived a great cataclysm, and after the fall there would have to have been no alternative but marriage to one's relations.

Descendants of these founding families would have no choice but to bear the consequences of a purely accidental selection of the founders' versions of genes. A fateful version that gets trapped in a founder population simply because the founding family happened to have carried it, will not be shed from that family so long as strangers cannot become spouses.

By itself, a disaster that leaves only a small sub-population alive usually does not assure a large family of people sharing the risky gene, because trapped genes will be dispersed into a larger population each time a family-member chooses a mate who is not descended from the founding families. But when the surviving sub-population has previously defined itself by rules that forbid such marriages to outsiders, then the problem of founder-effect inheritance may become severe.

But when all three requirements are met — a small founder population trapping one or more deleterious versions of genes, a strict adherence to endogamy for many generations, and great fertility during that long period – there will there be a significant population of people carrying the same deleterious mutation for this historical reason.

While the human species as a whole is not the product of any detectable founder effect more recent than its emergence as a species in Africa some millions of years ago – that is the meaning of the typically enormous variability of human genomes from one person to the next – there are many populations across the planet whose history makes them unexpectedly, invisibly, more like leopards than they know. For a person born into a founder-effect population, the data of DNA-based medicine may have specific but medically irrelevant meanings: DNA-analysis may lead to the recovery of family relationships that transcend the borders of language and appearance, and that mark one out in helpful or dangerous ways.

Membership in a group that defines itself by its behavior may thus become presumptive membership in a genetically-marked population. For people in this situation, any medical meaning of DNA-based diagnosis is shadowed by this fact. If the group shares versions of genes that are deleterious, and if the group has habits that maintain genetic isolation from the general population, then membership in the group may be seen by outsiders as tantamount to a disease in and of itself.

At such times, it is the duty of medicine to re-assert its initial meaning over the science that reveals the situation, and to protect such populations from serious potential non-medical consequences of a visit to the doctor.

Even though a founder-effect descendant's DNA may contain useful scientific data, and the DNA of such people is much sought after for research purposes, it should not be too easily given away. DNA-based information about a member of such a sub-population can be medically meaningful only if the person at risk can be safe in the choice to find it out. If the information is obtained in confidence, and is explained solely and completely in the context of the person's future risk, with a comprehensive and sensitive counseling on the possibilities of future problems, then it may be able to revert to medically useful information.

Even then, it is doubtful that there is a clear medical use for information about one's DNA-driven fate when there is nothing to do to deflect that fate. At such times DNA-based diagnostic information may have a greater meaning in political than in medical terms. DNA differences associated with disease set their carriers aside as a separate population for such political purposes as insurance rating, government or private employment risk or military service, or worthiness of receiving support for an expensive education.

Finally, such DNA-based information may have meanings within the endogamous founder population itself, revealing just how well or poorly the rules of endogamy have in fact been followed. All such purposes for reading a person's DNA cannot possibly make the acquisition of DNA-based information about the members of group medically – and thereby emotionally and religiously — meaningful. To confuse or elide the difference between a medical meaning and any of these others is to betray one of the moral obligations of medicine, at great potential cost to oneself, one's friends and one's family.

ARE JEWS A FAMILY?

It would be a mistake to think that misuses or abuses of diagnostic techniques for distinguishing one person's DNA from another's are a problem only for members of a founder population such as my own. Once again in this chapter I ask the indulgence of you all, as I use my own ancestors to illustrate a broad issue – in this case the risk that genetic information may have inadvertent, punitive uses. Thanks to the very facts of our species-wide shared genetic heritage, so clearly revealed at the DNA level, this issue is of deep relevance to everyone who thinks seriously about their future and their family's future, regardless of their religious preference, their degree of piety, or their scientific expertise.

We Jews call ourselves a family, and in many ways – for better and worse – we act as if we were. We continue to preserve common laws, habits, language, texts and historical memories, as well as the belief that all of these are the gifts of an unknowable Deity who began our place in history by exchanging covenantal promises with three successive generations of our ancestors, Abraham's, Isaac's, and Jacob's.

We have preserved these shared habits and beliefs for millennia, over a large fraction of the populated world. They are on the one hand the very model of strong memes in action, sometimes symbiotic, sometimes not; on the other, they exemplify the durability and reality of religious belief in the unknowable, and the survival of belief in the face of millennia of strong negative selective pressure. Do these facts mean that the Jews of today are a biological family as well, linked by descent from shared ancestors? Yes and no.

The Jews of centuries ago who codified prayers, understood that while being born a Jew was precious and important, it was not necessary and it certainly was not sufficient. The central ideas and actions of a Jew have always had to be taught and learned, they have never been inherited. Nevertheless, until about a decade ago, many reasonable people could still make the argument — in the absence of evidence to the contrary — that since Jews accept the covenants made with Abraham, Isaac and Jacob, the genomes of Jews must somehow be different from the genomes of all other people, containing unique versions of many genes; that is, that Jews are a biological family.

The difference between "are Jews a family" and "do Jews all share the same versions of one or more genes" is that the second form of the question has a testable, precise answer. As no two people have exactly the same version of the human genomic text, this claim could be confirmed or rejected by a search for versions of the human genome shared by all Jews and no other people.
Unfortunately the first group of scientists and doctors to pose the question in this way did so in a scientific context that reduced people to the bearers of their genomes, and in an inhumane manner that wound up being so painful, so cruel, and so lethal, that it is difficult to ask it again, even two generations after they were finally put out of business.
This context was the Nazi notion that despite all appearances to the contrary, every potential Jewish parent was inevitably the bearer of an undesirable, alien inheritance that would crush the true inheritance of Germany; in other words, the same idea that we have been asking about, the notion that Jews are a biological family. However inarticulately stated by Hitler's propagandists, this was the scientifically certified argument for the destruction by bullet, gas and fire of German and then European Jewry, of Germans and others who had one Jewish grandparent, and especially of about a million Jewish children, some of them born when I was born, in 1940.

THE DEMOGRAPHIC CONSEQUENCES OF A FOUNDER EFFECT: THE ASHKENAZIC JEWISH EXAMPLE.

In this historical context it is all the more remarkable that Jews all over the world flock to the new technology of DNA-based diagnosis, eager to lend their individual genomes – each a surviving data-point from the terrible experiment in negative selection — to a revisiting of this issue of biological Judaism. Fortunately this self-absorbed curiosity has provided sufficient genetic material to give a perfectly clear negative answer: there is no support in the genomes of today's Jews for the calumnious and calamitous model of biological Judaism. There are no DNA sequences common to all Jews and absent from all non-Jews, there is nothing in the human genome that makes or diagnoses a person as a Jew. But, as often happens when the tools of science are used in a medical context without a medical purpose, these same studies have raised unexpected difficulties in both medical, and religious, contexts.
Everyone will have to face similar difficulties sooner or later. To see what is coming in everyone's future, and to begin to understand how the Jewish experience may be helpful in heading off the worst possible outcomes for everyone else, it is necessary to know the demographics of the Jewish past. Numbers of Jews at various times in the past are not easy to get, and the ones we have are not precise. The best estimates I have been able to find show that in the long view, Jewish populations have enjoyed only a few periods of smooth, uninterrupted growth in any one part of the world.
From the earliest records to the admittedly partial documentation we have of numbers of Jews from different countries in the past five hundred years, a repeated pattern emerges of relatively brief periods of rapid population growth followed by instances of severe, almost complete population collapse, with long intervening periods of low but stable numbers. Each time a group of Jews survived one of these boom-and-bust cycles, it was as the descendants of a very small number; symbolically, as with the Jewish Patriarchs and Matriarchs, on just one family. Today there are about 6 billion people on Earth, and about 13 million of them are Jews. This means that about one person in 500, world-wide, is Jewish.
Three thousand years ago, upon David's establishment of the first Jewish nation-state, the Jewish population world-wide rose from about 500,000 to about 2 million, and for a while almost one person in 50, world-wide, was Jewish. But once Jerusalem fell to Babylon 2500 years ago, Jewish numbers declined back down to fewer than 300,000, and afterward, under Greek rule, the Jewish fraction of the population was once again reduced to about one in 500.
Numbers rose to about four or five million about 2000 years ago. They remained high, and for the first two Roman centuries, Jews were as many as one person in sixty. Then, as the world's population grew, the Jewish fraction fell once again, to about one person in 200 by the year 600. For the next millennium, until about 1600, the number of Jews remained about 1-1.5 million, while the world's population more than doubled. As a result the fraction of the world that was Jewish kept shrinking, until by 1600 it was back to the one in 500 that it was during the Babylonian exile.
Then an unexpected thing happened: a boom occurred in a fertile part of Europe and it did not go bust for almost 400 years. The Pale — a part of eastern central Europe now partially contained within the borders of Russia, Belarus, the Ukraine and Poland – let Jews live. The medieval Hebrew name for these European lands was Ashkenaz, and so Jews from that region still refer to themselves by the Hebrew plural Ashkenazim. Ironically, the place name derives from the name of one of the grandsons of Noah by his son Japheth, which suggests that the from the beginning, local inhabitants of this region were understood by their Jewish neighbors to be very distant relations indeed, not even the descendants of Noah's son Shem, the ancestor of Abraham.
For 400 years the Jews of Ashkenaz stayed put and grew in numbers. In that period — 1500 to 1900 — the total number of Jews worldwide went from about a million to about 11 million, and almost all of that increase took place in among the Ashkenazim. By 1900, one person in 150 worldwide was Jewish, and more than 90 percent of this greatest number ever, had descended from the Jews who had been living in central Europe since the 1500s. 1939 was the peak year for Jews in this world, who numbered between 16-17 million and were about one person in 120, world wide. All but about a million of them were descended from the original settlers of Ashkenaz, although the total number of Jews living there actually decreased in the early

twentieth century due to the emigration that brought my grandparents, among many others, to these shores.

The demographic losses of 1939-1945 may not be recoverable. In the last thirty years Jews worldwide have numbered about 13 million, neither growing nor shrinking by much. As the world's population booms, the Jewish slice of it shrinks. That is why today the fraction of the world's people who are Jewish – one in 500 or less – is no higher than it was 2500 years ago, after the first Babylonian exile.

My point in reviewing this set of population figures is not to raise the question of why, since David's kingdom fell, the world has been unable to bear more than one Jew in every five hundred people for longer than a century or so. Just the opposite: three times — after the fall of David and Solomon's kingdom 2500 years ago, after the fall of the Hasmonean Kingdom two thousand years ago, and in Ashkenaz after the pogroms and crusades and black death of the middle ages five hundred years ago — the total Jewish population actually grew, and in each case it grew more rapidly than the general population.

Of these three instances, the startling growth of the Jewish population in Ashkenaz is also the source of one of the world's largest founder-effects. In 1500, only a few percent — some tens of thousands — of the world's million or so Jews lived in the Ashkenazic Pale. By 1939, about 95% of the world's 17 million Jews either lived in Ashkenaz or were the descendants of people who had lived there until no more than fifty years earlier.

THE MEDICAL CONSEQUENCES OF A FOUNDER EFFECT

Combining the history of Ashkenaz with data from the genomes of their descendants alive today, we can get a good estimate of how few families founded today's Ashkenazic Jewish population. When people who carry an inherited condition are also the descendants of a single ancestor, their versions of the affected gene will be identical. If in addition they are the descendants of a population that practiced endogamy, then they will share more of their genome than that one gene with others suffering the condition.

Given the great number of versions of each gene available in the human species at large, long runs of identical versions of genes in two unrelated people will never occur by coincidence. But because the surviving population in Ashkenaz was so terribly small in the mid 1600s, and because it grew in an uninterrupted way from such small numbers, a large fraction of Jews today share such long stretches of genes with each other.

This was known in principle, but nevertheless the discovery a few years ago of identical stretches of DNA hundreds of genes long, in hundreds of apparently unrelated people from all corners of the world, was a surprise. The people who offered their genomes for this landmark study shared only two things: an inherited tendency to have one's muscles twisting one about – called Idiopathic Torsion Dystonia – and an ancestor who had come from Ashkenaz.

Most people in this study, but not all, called themselves Jews. Sometimes, though, members of an affected family would be shocked to discover that the inherited condition which had brought them into the study very likely meant an unexpected Jewish ancestry. With surprising regularity, when they understood the meaning of the tests done on themselves and their children, they would remember, admit – but not always accept – having Jewish ancestors.

The data from this study argued very strongly that the oddities of fate and the murderous intentions of strangers had fixed a history of near extinction four hundred years ago in the DNAs of the majority of Jews alive today. According to the scientists who carried out this study, the utter sameness of DNA in persons inheriting ITD world-wide means that every Jew whose ancestors come from Ashkenaz — about nine of every ten Jews alive today — is the descendent of one of no more than about 3000 families who survived the pogroms of the mid 1600s.

DISEASES OF THE ASKENAZIC BOTTLENECK ARE NOT JEWISH DISEASES.

It is terribly sad that Jews allow these marks of history to be called "Jewish diseases." As the chief Rabbi of London once famously said in response to an article in the London Times about the early-onset, lethal, incurable neurological condition called Tay-Sachs Disease, "There are no Jewish diseases," only the past consequences of violent ant-Semitism. Clearly, the shared genes of the Ashkenazim do not define any aspect of their Jewishness. Those descended from Ashkenazic ancestors share a higher-than-average frequency of versions of various genes, only because they are descended from the same survivors of Jewish Ashkenaz. The genomes of other Jews reflect their different histories. Descent from an Ashkenazic family, with or without its attendant inherited conditions, cannot make a person Jewish.

Those who see any aspect of Judaism as inherited, must be ignoring the demonstrated fact that Ashkenazim are a founder-effect family genetically quite different from the non-Ashkenazic families who make up most of the Jews of Israel. These Israelis would certainly fail any biological criterion set by Ashkenazic history, and vice-versa. Equally clearly, shared genes bring a shared fate: those Jews who do share a common Ashkenazic ancestry may not have inherited their Jewishness that way, but many have inherited a shared fate in the form of a genetic problem. Setting the particularities of Jewish history aside, then, let us look at a particular gene associated with an all-too-common late-onset disease, and at some of the medical and religious implications of what has been recently learned about both.

"Genetic disease" has as many meanings as "Family." The diversity of our species tells us that many different versions of each gene can be compatible with a healthy life. An unknown number

of other variant genes are wholly incompatible with embryonic development; inheritance of any of them leads to the loss of an embryo before birth.

In between are the variants of a gene that are compatible with birth, but not with the birthright we have come to expect, a life expectancy of around 80 years or more. Some of these variants are active in early life, causing infantile or childhood inherited diseases like Tay-Sachs. Other variant genes are not called upon by the body for much of a person's lifetime.

Still other variants may lack functionality but have no immediate consequence because a second copy of the gene is able to carry the work for both. When that sole copy of a functional gene is lost — and the older we get the more chance there is of a copy of a gene getting lost in one of our cells — the absence of a second functioning gene may show itself as a late-onset inherited disease, like inherited breast cancer.

DNA analysis can be used to find affected individuals in any of these different sorts of families. There are some good clinical reasons for seeking out these genes, and the people who carry them. Once the affected gene is recovered, it can be used to find the functional version from another person, and with that in hand the search for understanding how the normal gene works becomes straightforward science. Also, a working version may be used to repair the tissue damage caused by a non-functional gene. For instance, victims of cystic fibrosis who lack a fully functional version of the gene called CFTR have had their symptoms alleviated, at least for a time, by the administration of large doses of DNA encoding a functional human CFTR gene. On the other hand, members of families with a history of a late-onset inherited condition may find themselves obliged by the same technology to learn about their fate from their genomes at a time when they have no symptoms nor any expectation of treatment once the symptoms appear.

Cancer of the breast will afflict about one person in nine in this country. Each tumor begins as a mutation in a breast tissue cell. When an error in copying hits a critical gene, a cell is freed from the restrictions of differentiation and it begins to grow, forming a clone of mutated cells. Free growth is often accompanied by a loosening of a cell's editorial proofreading capacity, so that one mutation may beget another. In time a clone becomes a bump, the bump becomes a lump, and the lump becomes a spreading, dangerous tumor. About 75% of cases of breast cancer are sporadic. At this moment, these three-quarters of cases begin with mutations that have no known specific cause, whether genetic, hormonal, or environmental. A third of the remaining quarter of cases — about one in seven cases overall — occur in families with three or more generations of victims. Such families have inherited a clear susceptibility to the disease, and their tumors may well be the result of having inherited one or more nonfunctional variant genes. The causes of the remaining fifteen percent of cases are ambiguous, because neither family histories nor environmental histories are sufficiently clear to determine the likelihood of a pre-existing genetic risk or shared exposure to a known carcinogen.

BRCA1 AND BREAST CANCER: AN ASKENAZIC CASE STUDY

BRCA1 (BReast CAncer 1) is the first gene whose variants were found to be associated with familial breast cancer. Mutations in this gene were found by University of Utah scientists in breast-cancer victims from a number of unrelated Mormon families whose members suffered from a high incidence of breast cancer for three or more generations. BRCA1-associated cancer was reproducibly different from the more common, sporadic type: in addition to occurring in families, it appeared at a very young age, in both breasts, and in association with other cancers, especially of the ovaries. In such families, the link between cancer and the mutation is very high indeed: victims had an 86% chance of carrying a mutation in BRCA1. BRCA1 proved to be a very long gene, with lots of room for mistakes. More than 200 different mutations of BRCA1 have been recovered from different high-incidence families in the decade since the gene was first isolated and sequenced.

Ashkenazic Jewish families with a history of breast and ovarian cancer may also inherit a mutation in BRCA1. The founder effect of Ashkenazic history predicts that Ashkenazic families should have inherited only a few of the many known mutations in that gene; so far all Ashkenazic families with a history of breast cancer who do have a familial mutation in BRCA1 have been found to carry either one or another of only two of the 200 known mutations in BRCA1.

This simplicity makes Ashkenazic families in general a population of great interest both to scientists working on the details of how BRCA1 works in its normal and mutant states, and to genetic epidemiologists interested in setting up large-scale scans for single mutations. There has been a remarkable willingness on the part of Ashkenazic families – those who do not suffer from generations of breast cancer as well as those that do – to assist both these branches of science.

Not all the work these scientists wish to do, though, has any medical content. For instance, a 1997 paper in the New England Journal of Medicine reports a study in which scientists obtained the cooperation of hundreds of members of Ashkenazic families who did not have a family history of breast cancer, and checked their genomes for mutations in BRCA1. The results were a disturbing, unexpected and unwanted prophetic revelation through science. Two to three percent were carrying one of the two mutations.

This meant that even in the absence of any members with symptoms among members of two or three generations, and certainly in the absence of any symptoms in oneself, everyone in one of these families had a much higher risk of a bad fate than other people – even other Jews – who were not living out a founder-effect laid down by the violence of their ancestors' enemies. Statistically, each woman in a breast-cancer-free Ashkenazic family who is found to carry one of

the two mutations in BRCA1 has a greater that 50% chance of developing a breast tumor, and a 20% chance of developing an ovarian tumor.

What is to be done with these prophesies? They do not come to families prepared by a prior history of disease for news of an inherited condition. Rather, they come to healthy people – from unaffected families – on the wings of ancient and recent history, reminders that we are all not only the descendents of our grandparents, but also of their ancestors, people with whom we may think we have nothing in common.

We can be sure that prophetic news of this type – an unclear but high risk of a dread disease at a time when there are no family or personal symptoms — will not be reserved for long solely for Ashkenazic Jewish families. The difficulties lie not only in the discovery of a problem when you had no idea you were at risk; they lie in the wish to do the right thing, when there is no clear idea what that would be.

In the case of a BRCA1 gene there are only three options once one has found out one carries a mutation, and in the absence of a family history of the disease none alone justify submitting one's DNA to find out. Ovarian surgery means early menopause as well as sterility; prophylactic breast removal is a major operation and while it does lower risk, it does not remove it completely; and surveillance for the appearance of a breast tumor is something every woman should be doing anyway.

BIOLOGICAL JUDAISM: BAD SCIENCE, BAD RELIGION

I have argued that meaning and purpose are necessary, and that medicine as well as religion can be a source of meaning for the data of science. But even in religions with a long history of endogamy, the use of DNA data to make claims of inherited religious sensibility is inherently wrong. When those claims overlap medical issues, they allow for an extremely dangerous confusion to re-emerge from the ashes of history.

When medicine confuses religious faith with biological ancestry and science links biological ancestry to genetic difficulty, then it is but a small slippery step downward for medical practice to mark out member of a religious group as genetically defective, per se. The logic will be familiar, as will the threat of it, but this time the tools are available to uncover evidence of common ancestry, and of common genetic difficulties, in any population, world-wide.

Two immediate issues arise from the power of DNA analysis to uncover ancient common ancestries. One pertains to Israelis and their neighbors, and one to everyone. I might as well get to the first through a passage from Torah, because it is a really tough issue. From Genesis 25, lines 7-9:

> "This was the total span of Abraham's life: one hundred and seventy five years. And Abraham breathed his last, dying at a good ripe age, old and contented; and he was gathered to his kin. His sons Isaac and Ishmael buried him in the cave of Machpelah..."

It should not come as a surprise to learn – recall — that exiled Ishmael, circumcised patriarch of the twelve Arab tribes, rejoined his half-brother, the Jewish patriarch Isaac, to give their father a proper burial alongside Isaac's mother. If the tradition of descent from Isaac links Jews together despite the absence of biological confirmation for that ancestry, it must also link Jews forever with their Arab cousins.

One day the Jews of Israel will have to ask whether there can be an Israeli Law of the Return that makes sense while excluding the children of Ishmael. The only two countries that have a "law of the Return" are Israel, and Germany. In both countries, and in no others, a person born outside the country may receive citizenship on request by virtue of religion or “blood,” while other persons born inside the borders may not receive citizenship, for similar reasons. Israelis and Germans cannot tell each other how they should see their past, but Israelis certainly ought to think about why they are still in this tiny club.

SACRED DIVERSITY: THE RELIGIOUS MEANING OF COMMON ANCESTRY

The second implication of DNA-based diagnosis is for everyone to ponder: people — our species — are one family in precisely the same way that Jews are not. The story of Ashkenazic inherited diseases should make us all sensitive to the larger issues of inherited disease, and of genetic difference. Beyond the obligation this story tells us all to undertake — to accept the evidence and give up vain hopes of any religious birthright in their genes – is an even larger moral duty.

The moral context that gives meaning to science through medicine requires the attention of both science and medicine to a person in all his or her complexity and variability. The linkage of scientific medicine to religious history rather than to religious values may be more interesting in scientific terms, but it is fatally dangerous in medical terms.

Perhaps the best way to see the difference is to understand that though in social terms people tend to aggregate into groups of majority and minority populations — often separated by religion — by the data of our genomes we are all members of genetic minorities that range in size for the millions of a founder population, to the dozens of an immediate family, to the irreducible minority of one which is at the heart and soul of medicine. It would do us well to acknowledge that nothing in the legacy of human DNA blocks the choice to value the differences among us above the resemblance any of us might have to our idea of an ideal person.

By each of us exerting our free will to decide whether it is wise for us to know more or to know less about our own DNA at any given moment, the scientific data of DNA-based medicine may

be returned to a proper medical context. In light of the DNA evidence we already have, this means stretching the definition of normal variation to include the greatest possible diversity of inherited appearances and behaviors. Our obligation here is as clear in its own way, as the countervailing trend is in current medical science.

The straightforward agenda of scientists and the short-term acquiescence of physicians fifty years ago lead to the creation of the National Institutes of Health, each Institute named for a disease of the middle-aged white men in Congress who gave out Federal money in those days and still do today. These Institutes have provided the country and the world with much knowledge of great value, both medical and monetary. But with the creation of cheap, easy scans for mutations in genes like BRCA1, knowledge contributed by NIH-supported science has begun to change medicine in ways that deny the meaning medicine provides to science.

In "The Missing Moment"[2] I drew the following quote from my mentor and teacher, James D. Watson, discoverer of the structure of DNA and founding Director of the Human Genome Project. Writing in the Annual Report of his Laboratory, he had said:

> "If we could use genetic analysis to help work out the biochemical pathways underlying memory and clear thinking, for example, we might be able to find pharmaceutical compounds to improve these most needed human attributes. Thus, those who want to protect the mentally ill or the slow learner may not get what they strive for if they portray them exclusively as victims of their environment. We might like to think otherwise, but only by reducing the differences in human beings will we ever have a society in which we can effectively view all individuals as truly equal."

I admire Jim Watson for his unmatched taste in picking the right question to ask of nature as much today as I did when I first met him in the late 1960s, but I know that here he was deeply wrong. We know from a century and a half of research in ecology and evolution that as a species our future lies not in minimizing our differences, but in cherishing them. We know as well from millennia of religious insight that there is no possible way to justify any ranking of one person over another on grounds of any aspect of their physical being. From those two insights we have the chance of working toward a properly informed medicine, capable of using any and all insights from science in a context derived from the insights of many religions, and thereby capable of reducing all data to one purpose: to help people in need, one person at a time.

---

[2] Pollack, R., *The Missing Moment: how the Unconscious Shapes Modern Science*, New York, Houghton Mifflin, 1999.