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From Genomics to Epigenomics

Decades of sequencing and dissecting the human genome have confirmed that the real causes of ill health are environmental and social

It is not the genetic messages encoded in genomic DNA but environmentally-induced epigenetic modifications that overwhelmingly determine people's health and well-being Dr. Mae-Wan Ho

The Human Genome Project failed to deliver

Some of us had predicted that the US$ 3 billion project to sequence the human and other genomes would fail to deliver its extravagant promises [1, 2] (Genetic Engineering Dream or Nightmare, ISIS publication; Human Genome -The Biggest Sellout.in Human History, ISIS Report); and we were right [3] (Why Genomics Won't Deliver, *SiS* 26).

The Human Genome Project was followed by HapMap, a public-private research consortium dedicated to finding genetic variants that predispose people to common illnesses such as cancer, Alzheimer's and cardiovascular disease. HapMap was launched in Washington in 2002 [4], involving scientists and funding agencies from Japan, the UK, Canada, China, Nigeria, and the US. It would cost US$100million and take three years to complete. Francis Collins, who headed the Human Genome Project, and now Director of the US National Human Genome Research Institute (NHGRI), said: "The HapMap will provide a powerful tool to help us take the next quantum leap toward understanding the fundamental contribution that genes make to common illnesses like cancer, diabetes and mental illnesses." Companies like Affymetrix and Illumina developed powerful gene chips for scanning the human genome. Medical statisticians designed the genome-wide association study, a robust method for discovering 'true' disease genes and avoid the many false positives that have dogged the field [5].

In 2006, Elias Zerhouni, director of the US National Institutes for Health predicted that: "comprehensive, genomics-based health care will become the norm, with individualized preventive medicine and early detection of illnesses [6]. A year later, AmpliChip announced the new era of pharmacogenomics worldwide, as its test for cytochrome P450 genes can help drug providers prescribe selective serotonin reuptake inhibitors in the treatment of adults with depression [7]. The era of "genomics medicine" has arrived [8]; or has it?

The 1000 Genomes Project to the rescue

The reality behind the hype is something else. The lack of progress is such that in January 2008, the 1000 Genomes Project was announced [8]; its aim was to sequence at least 1 000 individual human genomes, and to look, again, for genetic susceptibilities to common diseases "at a resolution unmatched by current resources." Some of the HapMap organisations have committed major support to the new project: Beijing Genomics Institute in Shenzhen, China, the Wellcome Trust Sanger Institute in Cambridge, UK, and the NHGRI. Three US sequencing companies joined the consortium in June 2008: 454 Life Sciences, a Roche company in Branford, Conn, Applied Biosystems, an Applera Corp business in Foster City, California, and Illumina Inc., in San Diego, California.

The genomes of any two humans are more than 99 percent identical. It is hoped that the small fraction of genetic material that varies among people holds valuable clues to individual differences in disease susceptibility, response to drugs and sensitivity to environmental factors.

The 1000 Genomes Project is to build upon the HapMap comprehensive catalogue of human genetic variation organized into blocks called haplotypes. The HapMap catalogue laid the foundation for the recent [8] "explosion of genome-wide association studies that have identified more than 130 genetic variants linked to a wide range of common diseases, including type 2 diabetes, coronary artery disease, prostate and breast cancers, rheumatoid arthritis, inflammatory bowel disease and a number of mental illnesses."

However, the HapMap catalogue only identifies genetic variants present at a frequency of 5 percent or greater, while the 1000 Genomes Project catalogue will map many more details of the human genome and identify variants present at a frequency of 1 percent across most of the genome,and down to 0.5 percent or lower within genes. Francis Collins said it is like building bigger telescopes; "the results of the 1000 Genomes Project will give us greater resolution as we view our own genetic blueprint. We'll be able to see more clearly than before and that will be important for understanding the genetic contributions to health and illness." The project is estimated to cost around $60 million.

By June 2008, the 1000 Genomes Project has generated such vast quantities of data that the information is taxing the current capacity of public research databases. But information is not knowledge; genome sequences are telling us next to nothing on disease susceptibilities.

The "genomics medicine" that never was nor will be

By September 2008, David B. Goldstein at Duke University, a leading young population geneticist known partly for his research into the genetic origins of the Jews, said the effort to pin down disease susceptibility genes is not working.

There is absolutely no question that for the whole hope of personalized medicine, the news has been just about as bleak as it could be," he told the *New York Times* [5]. The HapMap and other techniques developed to make sense of the human genome was a "tour de force", but has produced only a handful of genes accounting for very little in explaining genetic predisposition to diseases: for schizophrenia and bipolar disorder, almost nothing, for type 2 diabetes, 20 variants that explain only 2 to 3 percent of familial clustering, and so on.

The reason for this disappointing outcome, in his view, is that natural selection has been far more efficient at eliminating disease-causing variants than people thought, so these variants are rare. It takes large, expensive studies with hundreds of patients in different countries to find even common disease variants, so rare variants are simply beyond reach.

It's an astounding thing," said Goldstein, "that we have cracked open the human genome and can look at the entire complement of common genetic variants, and what do we find? Almost nothing. That is absolutely beyond belief."

Goldstein is not alone in this bleak assessment of genomics. Concern has been raised for several years over commercially available gene tests offered to consumers, especially 'predictive genomic profiling' testing for variants in different combinations of genes for risks to illnesses such as lung cancer, type 2 diabetes or cardiovascular disease that are supposed to give people personalised nutrition and other life-style health recommendations.

Recently, researchers at Erasmus MC University Medical Center Rotterdam in The Netherlands critically appraised these genomic profiling now offered online by at least seven companies testing for variants in 56 genes. For 24 of the genes, there were no available studies to show that the profiling was useful in the general population. Of the remaining, only variants in 25 genes showed significant associations with risks in 28 diseases, but the associations were generally modest, and many of associations were with diseases unrelated to the condition for which the profiling was intended [10].

These weak associations most certainly *do not* mean that people carrying 'high' risk variants will definitely develop the disease, nor do they give licence to those carrying 'low' risk variants to adopt unhealthy lifestyles with impunity. As one critic commented [11], the genetic information provided by such direct to consumer genomics is "nearly all, to varying degrees, inaccurate, misleading or merely useless."

The real reasons genomics profiling fail, however, is not due to lack of data, or that natural selection is so effective in eliminating deleterious variants. It is the genomics project itself that is misguided.

Genetics to epigenetics

Critical voices had been raised against the genomics projects from within the scientific establishment since 2003; and soon afterwards, it became clear why genome sequences could tell us little about disease susceptibility, and much less, how to make designer babies. That's basically because the genome is fluid and dynamic, and impossible to pin down; the actions are predominantly in the 'hidden' parts of the genome that don't code for proteins, especially in *epigenetic* processes in response to the environment [3].

Even the conventional gene sequences that constitute only 1.5 percent of the genome are far from simple, as revealed by the findings of project ENCODE (Encyclopedia of DNA elements) organised by the NHGRI, and published in July 2007 [12]. ENCODE involved a consortium of 35 research groups that went through 1 percent of the human genome with a fine-tooth comb to find out exactly how genes work, and came up with some major surprises.

As Barry Patrick wrote of the ENCODE findings in *Science News* [13]: "genes are proving to be fragmented, intertwined with other genes, and scattered across the whole genome."

Indeed, within the human and other mammalian genomes, coding sequences are in bits (exons) separated by non-coding introns; and exons contributing to a single protein could be in different parts of the genome. Coding sequences of different proteins frequently overlap. Regulatory signals are similarly scattered upstream, downstream, within the coding sequence or in some other distant part of the genome [14] (see GM is Dangerous and Futile, *SiS* 40). The potential repertoire of proteins that can be made by combining different exons is perhaps a million times larger than the official number of about 20 000 genes identified in the human genome. *Which exons are recruited to make specific proteins depends entirely on the environmental contexts*.

Genome DNA sequences therefore really determine very little; it is the individual environmental experiences that overwhelmingly shape one's own health as well as the health of one's offspring, and possibly, the offspring's offspring.

Epigenetic inheritance *not* due to genomic DNA

The new discipline of *epi*genetics is the study of inheritance 'outside' genetics, i.e., not due to the DNA of the genome. This definition is the best I can think of that covers all examples to-date described in this series [15] (Epigenetics and Beyond series, *SiS* 41). It reveals how distinctly different proteins are assembled from separate exons and specific genes are marked to be expressed or not according to environmental context, how messages transcribed are altered, and even recoded in the genome; all of which were unthinkable to most people just a few years ago. These findings violate fundamental tenets of heredity, i.e., genetic determinism, that have dominated biology for a hundred years: the firm belief that the environment can never directly affect the genes, and characters acquired during one's life time cannot be inherited.

Epigenetics has put an end to genetic determinism; but by no mean supports environmental determinism. The hallmark of epigenetic inheritance is its dynamism and plasticity. Although the environmental epigenetic influence persists for varying periods of time, and can be transmitted across generations, it can also be reversed, or changed further by altering the environment in an appropriate way [16] (see Caring Mothers Strike Fatal Blow against Genetic Determinism, *SiS* 41).

Epigenetics is spawning its own databases to top all databases

Faced with the ever-expanding molecular complexities discovered soon after the human genome was sequenced, 'systems biology' was invented in academic institutions to curate a series of 'bio-informatics' databases all ending in 'omics': 'transcriptomics', for all RNA transcripts, the vast majority not coding for protein; 'proteomics', for all proteins translated; and 'metabolomics' for all metabolites made by chemical reactions in the body; in the vain hope that the true meaning of life will emerge from the data deluge [17] (No System in Systems Biology, *SiS* 21).

Now, more than five years later, 'epigenomics' is jostling for its own databases to top all databases. The Human Epigenome Pilot Project has begun with a consortium that includes the Wellcome Trust Sanger Institute in the UK, Epigenomics AG, a transatlantic biotech company with headquarter in Berlin, Germany, and the Centre National de Génotypage, a French Government research institute [18]. It aims to identify DNA methylation variable positions (MVPs) in the human genome. DNA methylation is only one among dozens of epigenetic mechanisms that alters the gene expression states or genetic messages in cells and tissues. The epigenome is an ever-changing, ever-evolving entity; there being potentially as many epigenomes as cells or tissues within a *single* organism, depending on the micro-environmental contexts. Indeed, monozygotic (genetically identical) twins do not always show the same disease susceptibilities; and it has been reported that young twins have similar DNA methylation whereas older twins differ considerably in both the amounts and patterns of DNA methylation [19], and most likely in other epigenetic markers acquired during the different individual experiences of each twin.

The epigenome of MVPs alone is unlikely to predict disease susceptibility as promised. At best, epigenomics may suggest appropriate environmental interventions for individuals after extensive and costly 'epigenomic typing'; and it is not clear that is feasible. Even if the capacity of current public databases could be expanded to accommodate these colossal catalogues, and all existing scientists were to be deployed in annotating and servicing the databases, it might still take more time than the age of the universe to search through them all.

Epigenetics confirms that the causes of ill health are overwhelmingly environmental and social and must be addressed by appropriate policies

Epigenetics is a new and exciting discipline, but the last thing it calls for is yet more mind-numbing cataloguing exercises and databases.

It has long been recognized that in stark contrast to the subtle effects of susceptibility genes, environmental effects swamp out even large genetic differences [1].

For example, toxic agents in the environment were found to scramble genome sequences to produce new transcripts linked to a range of chronic illnesses such Gulf War Syndrome, chronic fatigue syndrome, autoimmune diseases and leukaemia [20] (see Health and the Fluid Genome series, *SiS* 19). A new subdiscipline of Epigenetic Toxicology [21] (*SiS* 41) has emerged in recognition that toxic agents can have heritable epigenetic effects not only on individuals exposed, but also on their offspring

I can do no better than repeat my earlier warning that preoccupation with genomics and other 'bio-informatics' databases can only distract us from addressing the real causes of ill health [1-3], *which are predominantly environmental and social, as all the findings in the new discipline of epigenetics are telling us in no uncertain terms.*

To keep our genome, and much more so, our epigenome, healthy, we need a balanced ecosystem free from pollutants, we need to move away from industrial monoculture to a biodiverse, sustainable agriculture [22] (Food Futures Now *Organic *Sustainable *Fossil Fuel Free , ISIS publication). Sustainable agriculture free from chemical inputs and consumed locally is the only way to overcome both macronutrient and micronutrient deficiencies that compromise our physical and mental health, and our natural immunity against infectious diseases [23] (Unraveling AIDS, ISIS publication) We also need social policies that guarantee equal opportunities for all, and prevent the environmental deprivations we now know to have devastating epigenetic effects across several generations [16, 21].

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