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Epigenetics and the Autosomal DNA of Human Populations: Clinical Perspectives and Personal Genome Tests

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Abstract: Although the fields of direct-to-the-consumer DNA testing and genetic counseling have experienced rapid growth in the past five years in providing people with increasingly accurate analyses of their ancestry, admixture, family medical history and risk factors for disease, the subtle role of epigenetics in heredity has so far not been comparably exploited in medical research nor greatly appreciated by the wider public. The history of DNA testing in the consumer realm reveals a shift from sex-linked testing and easily traced Y chromosome and mitochondrial lines of descent to an emphasis on autosomal results, which are more diversified, complex and determinative. Matches showing ancestral relatedness are now possible to autosomal populations based on forensic science, ethnic strains and multi-generational markers, such as Native American and Jewish. Epigenetics, defined as the superstructure of genes, is beginning to be linked to population genetics to explore the environmental effect upon genes, nutrition and a host of transgenerational factors in susceptibility to diabetes, cancer, stress and other diseases or conditions. Specific areas discussed here are the Dutch Hunger Winter Study, methylation, cancer, stress, environmental toxins including fungicides and air pollution and neurological diseases. The emerging field of epigenetics with its emphasis on environment and nutrition is thus superseding the older model of genetic determinism in dictating people's health decisions, self-identity and ways of understanding their individual ancestry and ethnicity.

Keywords: Epigenetics, Autosomal DNA, Methylation, Chromatin Remodeling, Medicine, Longevity Studies, Genealogy

The story of DNA testing combines elements of religion, sex, biology, medicine, ethnicity, criminality, paternity, family and human evolution. DNA can be looked upon as the “language of God’s creation” as well as a potential instrument of eugenics and racism. It can be a means of discovering one’s roots in the absence of a paper trail, a breakthrough technology that is scientific rather than merely anecdotal (Hirschman and Panther-Yates 2006). But it has a dark side too. Popular perceptions are driven by what is dubbed genetic determinism, the belief that everything is in our genes.

In November of 2007, the preeminent scientific journal *Nature* trumpeted the headline, “Personalized genomes go mainstream: Companies prepare to offer a very personal service.” A story by Erika Check Hayden reported that two Silicon Valley start-ups intended to sell customers a lab test that would lay bare their entire genome. Popular interest in the Human Genome Project had now penetrated everyone’s consciousness. The secret of life has become one’s personal secret. But would owners of the new information have to disclose susceptibilities to genetic disorders to employers, relatives and insurance companies? What if genomics labs made mistakes in the raw data or interpretive results they supplied to customers? Did not this activity falsely feed into genetic determinism? Wasn’t the advent of eugenics close behind? DNA, as usual, was nothing if not controversial.

The first individuals to sequence their entire genomes were James Watson, co-discoverer of the structure of DNA, and Watson’s archrival for fame and glory, Craig Venter. Watson posted the six billion fragments of his genetic code on the Internet in 2007. Venter’s was published three months later. It included for the first time complete information on genes inherited from both mother and father—autosomal DNA.

Significantly, however, according to Harvard biology professor Richard Lewontin, because the Human Genome Project was completed by twenty or more research institutes, including Venter’s own Celera Genomics (which ran a parallel version of the project using more rapid

“shotgun sequencing” technology), much of its colossal achievement rested on computer guesswork. Before the appearance of the personal genomes of Watson and Venter, the Human Genome referenced by geneticists and health-care researchers was an artificial model corresponding to no living individual. Only by sequencing real human subjects and describing the vast variety of human genetics would medical science be able to achieve its aim of discovering the genetic basis of disease. Thus was born Phase II of the Human Genome Project, the conquest of disease and rare heritable disorders.

Phase II has had its own surprises. Watson fell from his pinnacle in October 2007 after making disparaging remarks in a British newspaper about the intelligence of Africans. The furor deepened when a fellow scientist announced that according to the personal genome Watson had released on the Internet, Watson himself was 16 percent Sub-Saharan African.

Historical Overview of DNA Testing

The scientific trend toward using genetics to study human diversity and biological relationships took root in the 1990s, when certain locations on the Y chromosome were identified as being of diagnostic use in typing male crime suspects (Butler 2010 pp 4-7). The same characteristic repetitive chemical motifs, called short-tandem-repeats (STRs) or alleles (variations), were found useful for determining paternity or maternity, as well as other relationships (e.g., sibling, cousin). Law enforcement today routinely uses autosomal profile matching to solve crimes and, sometimes, exonerate wrongfully convicted suspects. In 2010, Los Angeles police arrested 57-year-old Lonnie David Franklin Jr., whom they identified as the serial killer known as the Grim Sleeper on the basis of familial or relationship DNA testing.

- 1985 Alec Jeffreys invents DNA fingerprinting
- 1990s CODIS standard; GeneTree paternity testing
- 2000 Oxford Ancestors; Family Tree DNA
- 2003 Human Genome Project & PCR enhancements
- 2005 DNAPrint admixture test; National Geographic National Geographic; DNA Tribes; DNA Fingerprint Test
- 2008 Personal genomics (23&me); GWAS; blowback; economic downturn; immigration controversy
- 2009 DNAPrint failure; forensics crisis; 18 Marker Ethnic Panel
- 2012 Relationship or “cousin finder” tests

Figure 1: History of DNA Ancestry Tests

The techniques of tracing male and female descent are now generally accepted (Jobling and Tyler-Smith 2003; Sykes and Irven 2000; Richards and Macaulay 2000), with the nomenclature and phylogeny of male and female haplogroups having become standardized (Semino et al. 2000; Y Chromosome Consortium 2002; Richards et al. 2000; van Oven 2009). Further, a more powerful DNA testing approach – autosomal DNA analysis—has begun to throw light on all the “in between” areas of our genetic inheritance. This genotyping method examines markers that are spread across the twenty-two human chromosomes not linked to sex and has the potential to explore one’s total genetic inheritance, including deep, interwoven or hidden ancestry, not just

male or female demographic history. Autosomal technology targets 14 sites, a convention adopted in the United States in the mid-90s by the Federal Bureau of Investigation and termed Combined DNA Index System or CODIS markers (Butler 2006). Autosomes or genome-wide genetic systems have been adapted, among other applications, to study why indigenous American populations were susceptible to European disease; to explain early Homo Sapiens' triumph over Neanderthals; and even to set free wrongfully condemned inmates on death row.



Figure 2: Some DNA Companies

The Basis of Autosomal Ancestry Analysis: DNA Profiles

Autosomal DNA testing got off to a false start with so-called “biogeographical” products beginning around 2005. The first two such tests embraced by consumers were an admixture estimate called AncestryByDNA 2.5 co-invented by researchers at Pennsylvania State University and DNAPrint Genomics of Sarasota, Florida (Halder et al. 2008; Frudakis 2005; Shriver and Kittles 2004) and the DNA profile products independently developed by DNA Tribes (Arlington, Va.) and DNA Consultants on different platforms. DNAPrint ceased operations in 2008, and no “percentage product” has stood the test of time. Beginning in 2006, DNA Consultants, an academically-g geared company founded by Donald Yates, developed an autosomal DNA database for use in its in-house studies in Melungeon and Cherokee DNA, two of its specialties (Yates and Hirschman 2010). Called atDNA (*at* standing for autosomal), it is curated by Wendell Paulson, the company's statistics consultant, a faculty member in the Math and Natural Sciences Division of Arizona State University. The current version of atDNA 4.0 contains data on 400 world populations representing over 115,000 anonymous subjects' DNA profiling results from virtually all published forensic studies since 1996. In December 2011, DNA Spectrum joined the ranks of about half a dozen companies offering autosomal ancestry analysis. The term “biogeographical” faded from usage as familial and ancestral analysis relying on random match frequencies in population databases was exploited in a new generation of autosomal products.

Genetic System	Allele Designation
CSF1PO	11, 11
D2S1338	16, 24
D3S1358	16, 18
D5S818	11, 11
D7S820	9, 10
D8S1179	12, 14
D13S317	9, 13
D16S539	9, 13
D18S51	15, 18
D19S433	13, 14
D21S11	30, 32
FGA	20, 21
TH01	6, 9
TPOX	11, 11
vWA	19, 19

Figure 3: Sample Lab Report

In Figure 3, the scores in the column labeled Allele Designation represent pairs of values received from both parents. For example, in the locus known as FGA, where the allele reads 20, 21, the first number may have come from the mother, where it was part of her allele with another individual score (perhaps 20, 24) while the second number was inherited from the father (whose score on that allele may have been 21, 21). Alleles or variations at a given site combine to create an individualized DNA fingerprint. One’s DNA fingerprint is derived from one’s mother and father, theirs is derived from their parents, and so on. The DNA Fingerprint thus reflects both the mother’s and father’s genetic heritage—in fact, *all* one’s ancestry.

The basis of an autosomal match is random match probability, or RMP, a statistical measure of how common or rare a variant is in a given population. For instance, the chance to receive scores of 10 and 11 at one marker location is .16—16% of the population have 10 and 11 at that marker. In the next marker of the DNA profile, the frequency of that set of numbers may be .04 or 4%. To get the cumulative RMP for an entire DNA fingerprint, you multiply all the frequencies for loci together. Taking them all into account whittles the overall chance for a random person to have the same genotype to 1 in 7000, or 1 in a million, or 1 in a quadrillion, usually a very slight, remote possibility. For instance, a person’s cumulative profile values might

have a chance of 1.54×10^{-14} or .000000000000154 predictive frequency to appear in the population defined as Michigan Native American. The greater the probability of a person's values or alleles appearing in a population, the greater the presumption is that the person has ancestry in that population, as common configurations of allele results can only occur from reiterations or inheritance over generations. Autosomal markers seem to have a very low mutation rate. Through a diachronic lens, the mutation rates for the varying reported values of CODIS markers on any locus with which we have experience are very small (Butler 2010). The values appear to have been set from the beginning of mankind's expansion out of Africa and to have mutated little in the past 100,000 years. Diversity and relatedness are thus the effect of the historical processes of population structure, expansion and migration.

Populations, Metapopulations, Megapopulations and Ethnic Markers

Four hundred populations are aggregated into about 90 metapopulations and these are further combined into 21 megapopulations. As an example of a single metapopulation reflecting 21 constituent populations, see Fig. 5 (Native American). Although percentage, or admixture, results continue to elude DNA testing companies, DNA Consultants and DNA Spectrum have evolved what may be the next best thing. Megapopulations are the broadest ethnic categories calculated and reported by our database. The coverage and composition are described in Fig. 6.

Belem Amazonians (n = 325)
 Andean, Amazonian & Orinoquian (n = 846)
 Kichwas (n = 115)
 Guatemalan Mestizo (n = 200)
 Arizona - Apache (n = 99)
 Minnesota (n = 191)
 Alaskan Athabaskan (n = 101)
 Alaskan Inupiat (n = 109)
 Alaskan Yupik (n = 100)
 Arizona - Navajo (n = 93)
 Choles (Huichol) (n = 109)
 Florida (n = 105)
 Lumbee (n = 106)
 Michigan (n = 29)
 Minnesota (n = 303)
 Northern Ontario (n=292)
 Salishan (n = 151)
 Saskatchewan (n = 40)

Figure 5: American Indian Data Used in the Native American Definition.

African 17
 African American 28
 American Indian 24

Australoid 3
Austronesian 6
Central Asian 39
Central European 13
East Asian 39
East European 8
European American 24
Iberian 32
Iberian American 61
Jewish 3
Mediterranean European 20
Melungeon 1
Middle Eastern 36
North Asian 3
Northern European 15
Romani 4
South Asian 35
Southeast Asian 12

Figure 6: Megapopulation Names

Random match probabilistic prediction using the CODIS standard was first employed with paternity testing and forensic identification and has now been extended to familial, relationship and ancestry analysis. In 2009, DNA Consultants introduced autosomal ethnic markers, a deep-ancestry indicator also adopted by DNA Spectrum. These are eighteen markers that correlate at an incidence of 80% with probable ethnic ancestry as indicated (see Fig. 7, where a checkmark shows receipt of a marker from one or both parents, in other words, some degree of that ancestry).

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Marker	Allele	Allele
NATIVE AMERICAN I		
NATIVE AMERICAN II	✓	
EUROPEAN I	✓	✓
EUROPEAN II	✓	✓
EASTERN EUROPEAN I	✓	
EASTERN EUROPEAN II		
JEWISH I	✓	✓
JEWISH II		
JEWISH III		
JEWISH IV		
ASIAN I		
ASIAN II		
ASIAN III	✓	
ASIAN IV		
SUB-SAHARAN AFRICAN I		
SUB-SAHARAN AFRICAN II		
SUB-SAHARAN AFRICAN III		
SUB-SAHARAN AFRICAN IV		

Figure 7: Sample Ethnic Marker Results



Figure 8: Human Migrations

Using these eighteen deep-ancestry markers, it would be possible to present something like “the 60-second history of the human race.” But time and space prevent us from doing so here, for we must turn now to the next chapter in DNA testing, epigenetics.

Epigenetics

The term “epigenetics” was first used by Conrad Waddington in the 1940’s. Waddington merged the new knowledge about genes and genetics with embryology. “Epigenesis,” a concept that was around since Aristotelian time, described the study of embryological growth and differentiation. Epigenesis, then, addressed the biological imperative of cell differentiation where, while each cell contains the same DNA, cells develop into specialized tissues and organs that are unique. The integration of the concepts of epigenesis and genetics gave origin to the term epigenetics. Waddington’s intent with epigenetics was to provide insight into gene-environment interactions that influence development and embryology (Holliday 2006):

Today, epigenetics is being studied to explain the environmental effects upon genes and how that influences disease. This avenue of research is all the more exciting because mere genes have not satisfactorily explained modern epidemics of heart disease, obesity, Type 2 diabetes, cancer, and autism, and epigenetics is shedding light on the environmental factors that change the way our genes function, to promote, or prevent these and other disease processes (Genuis 2012; Slomko et al 2012; Jirke, Skinner 2007).

“Epi” literally means “above”. Thus, epigenetics refers to the influences “from above” that affect the DNA. Epigenetics refers to modifications to DNA and chromatin (the protein scaffolding that surrounds the DNA) that persist from one cell division to the next despite a lack of change in the underlying DNA sequence (*i.e.*, a mutation). The “epigenome,” then, refers to

the interface between the environment and the genome. In fact our entire environment is having a conversation with our entire genome 24 hours a day. This is the basis behind the new science of epigenetics – how the environment affects the cellular DNA.

Cells are bathed continuously in a sea of changing environmental conditions. This means the epigenome is dynamic and responsive to environmental signals – especially during human development – but also throughout life. It is becoming increasingly apparent that stress, environmental chemicals, and nutrient deficiencies are some of the biggest factors that promote epigenetic changes to the DNA. In addition, some of these changes in gene expression persist long after the exposure has stopped. This means that such changes can transcend generations.

Researchers at the University of Pittsburgh stated in the journal *Medical Hypotheses* in 2009:

“It is becoming clear that a wide variety of common illnesses, behaviors, and other health conditions may have at least a partial epigenetic etiology, including cancer, respiratory, cardiovascular, reproductive, and autoimmune diseases, neurological disorders such as Parkinson’s, Alzheimer’s, and other cognitive dysfunctions, psychiatric illnesses, obesity and diabetes, infertility and sexual dysfunction. Effectors of epigenetic changes include many agents, such as heavy metals, pesticides, tobacco smoke, polycyclic aromatic hydrocarbons, hormones, radioactivity, viruses, bacteria, basic nutrients, and the social environment, including maternal care. It has even been suggested that our thoughts and emotions can induce epigenetic changes.”

While modern health care has made enormous strides in emergency and trauma care, and infectious disease control, most of modern day illnesses are chronic in nature (<http://www.cdc.gov/chronicdisease/> accessed 6/30/12). Our lifestyles have changed drastically over the last 100 years and yet 100 years is not nearly long enough for our DNA to change appreciably in adaptation to our environment. These lifestyle changes include dietary changes from organic (before the 1940s all food was organic because pesticides and herbicides had not been invented yet), unprocessed foods to processed, low nutrient density, mineral poor, pro-inflammatory diets. It is interesting to note that the same three known DNA modifiers – poor nutrition, ever-increasing stress levels, and exposure to environmental toxins – are also linked to increasing incidences of cancer, obesity, Type 2 diabetes, auto-immune diseases, and all chronic diseases in westernized countries (Pereira Barbachano et al. 2007).

Nutritional status across the life time is now recognized as an important modulator of human health and chronic disease risk. These complex relationships derive from studies on plasticity in developmental biology that are traceable to environmental effects (Gluckman, Hanson et al. 2005). Food is comprised of bioactive compounds that influence epigenetic profiles by altering DNA methylation or histone modification, or by influencing the sufficiency or insufficiency of dietary substrates that are necessary for these enzymatic processes (Choi, Friso 2010).

Nutritional status influence is most important during pregnancy, as evidence from many studies suggest that nutritional experiences during critical periods of fetal development have epigenetic effects that persist throughout the life course (Zeisel 2009). As one example, a recent study in rats found that a low-protein maternal diet during early pregnancy predisposed the offspring to Type 2 diabetes due to epigenetic modification (Sandovici, Smith et al 2011). One of the largest natural, albeit tragic, experiments that demonstrate the effect of nutritional exposure on human development is the “Dutch Hunger Winter”.

During World War II the Dutch experienced a Nazi induced famine during 1944-45 due to a blockade of food. This diet, which restricted calories to 400-800 calories per day even for pregnant women has yielded many research insights into the epigenetic effects of famine during pregnancy.

One of the most interesting observations from the Dutch Hunger Winter Study was that dietary deprivation of pregnant mothers that resulted in long-lasting consequences for adult

health did not necessarily result in variations in birth weights. Women exposed to famine during the middle and late months of pregnancy had babies with significantly reduced birth weights. But babies born to mothers who were exposed to dietary deprivation only during early gestation (and the blockade ended prior to them giving birth) had normal birth weights, due to intrauterine catch up growth, but still grew up to have higher rates of obesity than those born before and after the war, and those exposed to famine mid to late pregnancy (Schultz 2010).

A deprived fetal environment followed by an abundance of food in childhood may be a recipe for adult chronic disease. This is strikingly shown by comparing babies born to Dutch mothers during or shortly after the famine, where food supplies were quickly replenished, and babies born during or shortly after the siege of Leningrad where food supplies were not so quickly replenished. In the case of the Leningrad babies who continued to have restricted nutrition and calories for a few years, no increase in obesity or cardiovascular disease was seen in adults (Schultz 2010). This suggests that intrauterine or infant/childhood catch up growth in times of abundance actually has a counterintuitive effect on health by promoting adult chronic diseases such as obesity and cardiovascular disease.

In the case of cancer, a rising epidemic in our society, the presence of genetic lesions alone has been found to be insufficient for tumor formation. Rather, cancer is a multistep process dependent on crosstalk between genetic alterations and epigenetic influences from the environment (Su, Mahabir, et al. 2011). Diet, stress, and environmental toxins are all epigenetic factors in the development of cancer.

The observation that epigenetic changes are reversible makes them an appealing target for cancer and other disease prevention, as well as for optimal fetal and child development.

The recent body of literature demonstrating association between air pollution and cancer, underscores the significance of the reversibility of epigenetic influences from the environment. The relationship between higher air pollution and underdeveloped and developing countries, where environmental regulations tend to lag behind the developed countries, and poor, inner city areas, is a clear case of disparity in health outcomes based on modifiable environmental influences.

Air pollution and population health currently stands as one of the most important environmental and public health issues of our times. Air pollution levels in developed countries have been decreasing dramatically in recent decades, although still remains high in certain cities and along congested freeways. However, in developing countries like China and Southeast Asia, air pollution levels are still at relatively high levels. In recent years, several hundred epidemiological studies have emerged demonstrating adverse health effects associated with exposure to the particulate matter and gases found in air pollution.

A recent study in Los Angeles, California highlighted the association between mothers who lived in areas with higher levels of air pollution and the rates of childhood cancer in their children, with the mothers who lived in lower levels of air pollution. An association was found in the mothers who were exposed prenatally to more particulate matter from the higher levels of air pollution, and higher rates of cancer in their children (Heck and Wu 2013).

Similarly, China, which has been plagued with high levels of air pollution, found an association with the development of breast cancer in women due to the particulate matter in air pollution acting as a foreign estrogen (xenoestrogen) in the women's bodies (Qiang and Zhang 2013). A very large meta-analysis of air pollution and lung cancer in Europe demonstrated a link as well (Raaschou-Nielsen and Andersen 2013).

These findings indicate the need for preventive efforts to address these modifiable environmental effects on cancer incidence in developing countries, and also in inner cities and residential areas in close proximity to congested freeways. Air pollution stands out as an environmental factor that is perfectly amenable to intervention. According to the World Health Organization:

“Significant reduction of exposure to air pollution can be achieved through lowering the concentrations of several of the most common air pollutants emitted during the combustion of fossil fuels. Such measures will also reduce greenhouse gases and contribute to the mitigation of global warming.” (www.who.int/mediacentre/factsheets 2011).

The evidence that health disparities trace their origin to environmental rather than genetic factors comes from an extensive literature base documenting the deleterious health impacts of economic and status inequality, such as stress or discrimination (Thayer and Kuzwara 2011). While research already supports the connection between blood pressure, stress hormone regulation, immune function and stress, work is now being done to evaluate stress induced durable epigenetically-based changes in gene regulation that relate to changes in physiology and behavior. For example, chronic stress in adult mice leads to demethylation of the gene that encodes a stress hormone that predicts stress-induced social avoidance (Thayer and Kuzawa 2011).

Human studies have implicated disrupted methylation, an epigenetic process, in imprinting and neurological diseases (Fernandez, Assenov. et al 2012). Recent animal and human data have suggested that early-life adversity leads to epigenetic regulation of genes involved in stress-response systems.

This is significant because for social, economic, and environmentally disadvantaged groups, these childhood and even fetal experiences with stressful situations can have lifelong consequences in learning, behavior, and mental health, let alone other medical and health outcomes. Indeed, these epigenetic imprints can even extend their effects for several generations.

Rats that were less nurtured as newborns had an altered epigenome that resulted in more anxiety as adults (Weaver and Cervoni 2004). Furthermore, maternal under-nutrition or stress is associated with low birth weight, leading to an increased risk of metabolic and cardiovascular illness in the offspring via epigenetic programming of the hypothalamic-pituitary-adrenal (HPA) axis (Meaney, Szyl, et al 2007). Other research supports the epigenetic contribution of early life stress (childhood abuse, neglect, and loss) on the development of depressive disorders later in life (Heim and Binder 2012). Suicidal behavior has also been linked to epigenetic changes in genes regulating the stress-response systems (Turecki, Ernst et al. 2012) Thus, environmental adversity alters maternal physiology and behavior, which then programs HPA activity in the offspring. The good news in these studies is that these epigenetic changes are potentially reversible.

Epigenetic processes are designed to rapidly respond to environmental conditions and by doing so allow modifications to an adverse environment, such as stress. It is now being understood that human complex diseases, including psychiatric and disorders relating to biochemistry and nutrition, are related to trans-generational epigenetic inheritance of maladaptive responses to environmental stress (Zucchi, Yao et al. 2012) The Figure below depicts how this occurs.

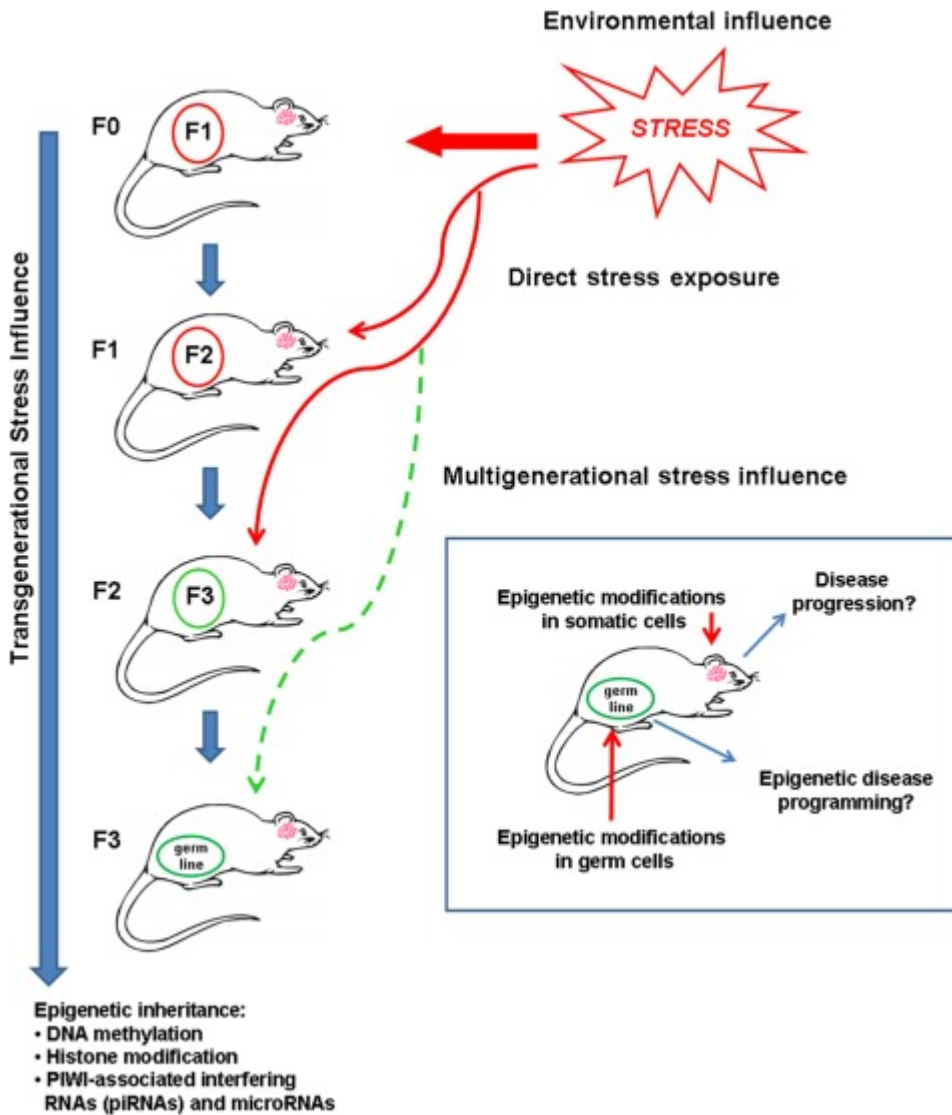


Figure 4: Transgenerational Effects of Stress

Source: *Front Genet* 2012;3:96

Inheritance of an epigenetic memory caused by an adverse environment, such as stressful experiences, produce phenotypes in next generations that may influence disease risk. Solid red arrow indicates direct exposure to stress in an animal; thin red arrows indicate direct stress exposure leading to intergenerational stress influence in F1 and F2 generations; dashed thin green arrow indicates possible transgenerational inheritance of a multigenerational stress phenotype in the F3 generation. To prove genuine epigenetic programming, it is necessary to determine phenotype transmission to the third generation (F3).

A literature base documenting the role of environmentally induced epigenetic changes to biological function and health is expanding rapidly. For example, studies have found that higher concentrations of persistent organic pollutants (POPs) are linked to a decrease in global

methylation, an epigenetic process often leading to cancer, in humans (Kim, Kim, et al. 2008; Rusieki, Baccarelli et al. 2008).

As with nutritional exposures and stress, environmental toxin exposure during pregnancy has been shown to influence the offsprings' epigenetic profile leading to predisposition to certain diseases. For example, smoking during pregnancy modifies histone proteins, an epigenetic process, that changes gene expression to a pro-inflammatory state in offspring (Prescott 2011). In addition to prenatal smoking, it has also been shown that exposure to car exhaust causes other epigenetic modifications that predisposes the child to asthma (Durham, Wiegman, et al. 2011). These studies and others are groundbreaking because they show for the first time that prenatal exposures to environmental toxins can modify epigenetic markings in offspring, thereby modifying risk factor for various diseases *even prior to birth*.

Another significant study found that mice exposed once to a popular fungicide during gestation resulted in abnormal methylation patterns in sperm which led to adverse effects on reproductive function persisting for at least three generations (Anway and Skinner 2008). Another study looked at the same common-use fungicide (vinclozolin) and discovered that it epigenetically modified three generations of mice to have altered physiology, behavior, and metabolic activity in discrete brain regions which caused them to respond differently to chronic stress (Crews and Gillette 2012).

The emerging field of epigenetics is superseding genetic determinism in explaining health and disease in animal and human populations. Genes load the gun, but it is the environment that pulls the trigger.

REFERENCES

- Anway, M.D. and M. K. Skinner. "Epigenetic Programming of the Germ Line: Effects of Endocrine Disruptors on the Development of Transgenerational Disease." *Reprod Biomed Online* 16/1 (Jan 2008):23-5.
- Butler, John M. "Genetics and Genomics of Core Short Tandem Repeat Loci Used in Human Identity Testing." *Journal of Forensic Science* 51/2 (2006):253-65.
- , *Fundamentals of Forensic DNA Typing*. Amsterdam: Elsevier, 2010.
- Choi S.W. and S. Friso "Epigenetics: A New Bridge Between Nutrition and Health." *Adv Nutr*;1/1(2010):8-16.
- Crews D. et al. "Epigenetic Transgenerational Inheritance of Altered Stress Responses." *Proc Natl Acad Sci U S A* 109/23 (2012):9143-48.
- Durham A.L. et al. "Epigenetics of Asthma." *Biochim Biophys Acta* 1810/11 (2011):1103-9.
- Fernandez A.F. et al. "A DNA Methylation Fingerprint of 1628 Human Samples." *Genome Res* 22/2 (2012):407-419.
- Frudakis, Tony N. "Powerful but Requiring Caution: Genetic Tests of Ancestral Origins." *National Genealogical Society Quarterly* 93/4 (2005):260-28.
- Genuis S.J. "What's Out There Making us Sick?" *J of Environ Public Health* 2012:605137 (2012).
- Gluckman, P.D. et al. "Towards a New Developmental Synthesis: Adaptive Developmental Plasticity and Human Disease." *Lancet* 373/9675 (2009):1654-57.
- Halder, I.M et al. "A Panel of Ancestry Informative Markers for Estimating Individual Biogeographical Ancestry and Admixture from Four Continents: Utility and Applications." *Human Mutation* 29/5 (2008):648-58.
- Hammer, M.F. et al. "Extended Y Chromosome Haplotypes Resolve Multiple and Unique Lineages of the Jewish Priesthood." *Human Genetics* 126 (2009):707-17.
- Hayden, Erika Check. "Personalized Genomes Go Mainstream; Companies Prepare to Offer a Very Personal Service." *Nature*, vol. 450/ 7, 166 (November 2007):11.
- Heck, J.E. et al. "Childhood Cancer and Traffic- Related Air Pollution Exposure in Pregnancy and Early Life." *Environ Health Perspect* 121/11-12 (2013):1385-91.
- Heim, C and E.B. Binder. "Current Research Trends in Early Life Stress and Depression: Review of Human Studies on Sensitive Periods, Gene-Environment Interactions and Epigenetics." *Exp Neurol* 233/1 (2012):102-11.
- Hirschman, Elizabeth C. and Donald N. Yates. "Romancing the Gene: Making Myth from Hard Science," in *Handbook of Qualitative Research in Marketing*, ed. Russell W. Belk, pp. 419-29. New York: Edward Elgar, 2006.
- Holliday R. "Epigenetics: A Historical Overview." *Epigenetics* 1/2 (2006):76-80.
- Jirtle, R.L. and M.K. Skinner. "Environmental Epigenomics and Disease Susceptibility." *Nat Rev Genet* 4 (2007):253-62.
- Jobling, M. A. and C. Tyler-Smith. "The Human Y chromosome: an Evolutionary Marker Comes of Age." *Nature Reviews Genetics* 4 (2003):598-612.
- Kim K.Y. et al. "Association of Low-Dose Exposure to Persistent Organic Pollutants with Global DNA Hypomethylation in Healthy Koreans." *Environ Health Perspect*. 118/3 (2010):370-74.
- Lewontin, Richard C. *Biology as Ideology: The Doctrine of DNA*. New York: Harper Perennial, 1993.
- Meaney, M.J., et al. "Epigenetic Mechanisms of Perinatal Programming of Hypothalamic-Pituitary-Adrenal Function and Health." *Trends Mol Med*. 13/7 (2007):269-77.
- Pereira, F, et al. "Vitamin D has Wide Regulatory Effects on Histone Demethylase Genes." *Cell Cycle*. 11/6 (2012):1081-89.

- Prescott, S., and R. Saffery. "The Role of Epigenetic Dysregulation in the Epidemic of Allergic Diseases." *Clin Epigenetics* 2/2 (2011): 223-232.
- Qiang, H. et al. "Effects of Ambient Particulate Matter on Human Breast Cancer- is Xenogenesis Responsible?" *PLoS One* 8/10 (2013):e76609.
- Raaschou-Nielsen, O. et al. "Air Pollution and Lung Cancer Incidence in 17 European Cohorts: Prospective Analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE)." *Lancet Oncol* 14/9 (2013):813-22.
- Richards, M. and V. Macaulay. "The Mitochondrial Gene Tree Comes of Age." *American Journal of Human Genetics* 68 (2000): 1315-20.
- Richards, M. et al. "Tracing European Founder Lineages in the Near Eastern mtDNA Pool." *American Journal of Human Genetics* 67 (2000): 1251-1276.
- Rose, Steven Peter Russell, Richard C. Lewontin, Leon J. Kamin. *Not in Our Genes. Biology, Ideology and Human Nature*. New York: Penguin, 1990.
- Rusiecki, J.A. et al. "Global DNA Hypomethylation is Associated with High Serum-Persistent Organic Pollutants in Greenlandic Inuit." *Environ Health Perspect* 116/11 (2008):1547-52.
- Sandovici I. et al. "Maternal Diet and Aging Alter the Epigenetic Control of a Promoter-Enhancer Interaction at the Hnf4A Gene in Rat Pancreatic Islets." *Proc Natl Acad Sci USA* 108/13 (2011):5449-54.
- Schultz L.C. "The Dutch Hunger Winter and the Developmental Origins of Health and Disease." *Proc Natl Acad Sci USA* 107/39 (2010):16757-8.
- Su L.J. et al. "Epigenetic Contributions to the Relationship Between Cancer and Dietary Intake of Nutrients, Bioactive Food Components, and Environmental Toxicants." *Front Genet.* 2/91 (2011).
- Slomko, H. et al. "Minireview: Epigenetics of Obesity and Diabetes in Humans." *Endocrinology* 153/3 (2012):1025-30.
- Shriver, M. D. and R. A. Kittles. "Genetic Ancestry and the Search for Personalized Genetic Histories." *Nature Reviews Genetics* 5 (2004): 611-618.
- Sykes, Bryan. *Saxons, Vikings, and Celts. The Genetic Roots of Britain and Ireland*. New York: W.W. Norton, 2006.
- . *DNA USA. A Genetic Biography of America*. New York: Liverwright, 2012.
- Thayer, Z.M. and C.W. Kuzawa. "Biological Memories of Past Environments." *Epigenetics* 6/7 (2011): 1-6.
- van Oven, M. and M. Kayser. "Updated Comprehensive Phylogenetic Tree of Global Human Mitochondrial DNA Variation." *Human Mutation* 30/2 (2009):E386-E394.
- Nicholas Wade. *Before the Dawn. Recovering the Lost History of Our Ancestors*. New York: Penguin, 2007.
- Turecki, G. et al. "The Neurodevelopmental Origins of Suicidal Behavior." *Trends Neurosci.* 35/1 (2012):14-23.
- Watson, James D. and Andrew Berry. *DNA: The Secret of Life*. New York: Knopf, 2004.
- Wells, Spencer. *Deep Ancestry. Inside the Genographic Project*. Washington: National Geographic, 2006.
- Y Chromosome Consortium. "A Nomenclature System for the Tree of Human Y-Chromosomal Binary Haplogroups." *Genome Research* 12 (2002):339-48. Updated in Karafet, Tatiana M. et al. "Human Y Chromosomal Haplogroup Tree." *Genome Res.* published online April 2, 2008.
- Yates, Donald N. and Elizabeth C. Hirschman. "Toward a Genetic Profile of Melungeons in Southern Appalachia." *Appalachian Journal* 38/1 (2010):92-111.
- Ziesel, S.H. "Epigenetic Mechanisms for Nutritional Determinants of Later Health Outcomes." *Am J Clin Nutr* 89/5 (2009):1488s-1493j.

Zucchi, F.C. et al. "The Secret Language of Destiny: Stress Imprinting and Transgenerational Origins of Disease." *Front Genet* 3/96 (2012)

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