Genetics and the Life Course

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Abstract

A life-course perspective is committed to the proposition that from conception to death, all human outcomes are the result of a continual interaction between the individual and all of the environments that he or she inhabits at any given point in time. Early development is a critical period, a window of time during the life course when a given exposure can have a critical or permanent influence on later outcomes. But the impact of exposures upon outcomes does not end at any specific point in time, inasmuch as life is a continuing interactive and adaptive process. We now know that what applies to human beings also applies to their genomes. The "outcome" of any gene at any given point in time (whether or not it is used to transcribe a particular protein, what form of that protein, and how much) is a product of the interaction between the gene and the multiple environments of which it is a part, which include the epigenome, the cell, the biological human, and the assorted environments he or she occupies (e.g., geographical, socioeconomic, ethnic, etc.). Early life experiences can permanently "reprogram" the epigenome and gene transcription with life-long behavioral consequences. At the same time, the epigenome as well as the genome continue to be environmentally responsive throughout the life course.

INTRODUCTION

In the most general sense, a life-course perspective is committed to two propositions: First, that from conception to death, all human "outcomes" or phenotypes (health, disease, psychology, behavior) are the result of a continual interaction between the individual and all the environments that she inhabits at any given point in time. These environments are always nested, multiple, and interactive. An embryo occupies the environment of the mother's womb, which occupies the environment of the mother's body; the mother occupies an environment at once familial, socioeconomic, ethnic, cultural, and geographic. To understand human outcomes we must take into account the potential impact of all of these interconnected environments. Thus characterized, a life-course perspective encompasses a developmental approach. Second, human life is an ongoing interactive process and change—environmental and biological—continues from conception to death

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and the trajectory of any given stage of development will be influenced by the preceding stages. Hence, the need to look at the life *course* as opposed to a snapshot view of the individual at any given point in time.

How does genetics fit into a life-course perspective? As we shall see, to understand the relationship between genetics and outcomes (or phenotypes) we must adopt the same stance toward the gene that we do toward the person: In sickness and in health, in normal and abnormal development, the "behavior" of genes or genomes cannot be understood apart from the nested environments in which they are located. Hence, by necessity, any consideration of genetics from a life-course perspective encompasses much more than the physical presence and structure of a gene, whether one gene or one thousand. As in the case of the biological person, the genome itself (or rather genomes, because persons possess more than one) changes throughout the life course. Hence, the need to consider the "life course" of the genome itself. It is important to note that what is here characterized as "genetics and the life course" is based on cutting-edge research in molecular genetics and recent discoveries that are overturning many traditional dogmas.

A gene is a segment of DNA that contains information that can be used, by the cell, to construct amino acids, the building blocks of proteins. In the process known as gene *transcription*, a segment of DNA is copied to produce messenger RNA, which serves as a template for the synthesis of protein. In structures called *ribosomes*, the messenger RNA template is used to form a particular protein in a process known as *translation*. Persons inherit at least two copies of a gene, one from each parent. Each copy of a gene is called an *allele*, and alleles from both parents may be identical or they may differ slightly. These *structural* differences between alleles can be found in many different configurations or versions. When two or more versions of an allele for a gene occur in >1% of a given population, it is referred to as a *polymorphism*. A version of an allele that occurs in <1% of the population is called a *mutation*. A *genotype* refers to the specific alleles one possesses, and all of one's inherited alleles are her genome. It is common to speak of a (single) genome, but as we shall see, all persons possess multiple genomes.

INHERITANCE

The life course of the genome begins before conception in the gametes: the egg cell or oocyte supplied from the mother and the sperm cell from the father. Each gamete supplies half of our full complement of chromosomes and half of our alleles. Genes, however, are by no means the only biological agent of inheritance. From our mothers we also inherit, via the oocyte, assorted nutrients, abundant messenger RNAs, noncoding RNAs (RNA molecules not involved in translation) and a variety of organelles, structures

within a cell that perform essential cellular functions. From sperm, we inherit, in addition to half our DNA, messenger RNAs and noncoding RNAs, as well as an organelle known as a *centrosome*, which facilitates cellular division and plays a key role in human fertility and the ability of embryos to undergo normal development (Chatzimeletiou, Morrison, Prapas, Prapas, & Handyside, 2008).

Among the organelles we inherit are mitochondria, which perform essential cellular functions including the generation of cellular energy. mtDNA (mitochondrial deoxyribonucleic acid) is inherited solely from the mother inasmuch as mitochondria from sperm are destroyed shortly after fertilization. Mitochondria contain multiple copies of their own DNA molecules—mtDNA—that are distinct from the more familiar *nuclear* DNA contained in the nuclei of all of our cells. Oocytes from the same mother may contain anywhere from 11,000 to 903,000 mtDNA molecules per oocyte, and mitochondrial number, distribution, and structure play essential roles in fertilization and normal embryonic development. Studies indicate that the mean number of copies of mtDNA in human fertilized oocytes is ~250,000, while for unfertilized oocytes, the mean is 164,000, and it has been suggested that a mitochondrial complement of at least ~100,000 copies of mtDNA is required for normal embryonic development (Shoubridge & Wai, 2007).

A number of different factors have been shown to influence both the number of mitochondria (and hence the amount of mtDNA) and the manner in which mitochondria function post-fertilization. Maternal fertility declines rapidly from a peak conception rate at age 22. In addition to having fewer eggs ovulating, the "quality" of a woman's eggs declines; and one of the contributing factors is a loss of mitochondria due to the accumulation of age-dependent mutations of mtDNA (Jones & Lopez, 2013). With age, there is also an increase in mutations in the oocyte's nuclear DNA and by age 40, half of a woman's eggs are chromosomally abnormal (the nuclear DNA is contained in the chromosomes), and 2 years later this figure rises to 90% (Jones & Lopez, 2013). One common chromosomal abnormality is trisomy, three copies of a particular chromosome, and depending on the chromosome affected, the result can be a number of different "trisomic" disorders in offspring.

After ovulation, the oocyte enters a state of arrest during which DNA transcription stops and after fertilization transcription does not begin until after the embryo reaches the two-cell stage, when transcription commences via a process known as embryonic genome activation (EGA). How can an embryo develop during this period with a nonfunctioning genome? The answer is that while transcription is stopped during this period, *translation*, the synthesis of proteins from messenger RNA, is not. The oocyte contains a vast array of messenger RNAs that are translated into proteins in the

ribosomes (which are also inherited with the oocyte). Messenger RNAs are also present in smaller amounts in sperm and their translation pre-EGA is almost certainly critical for normal development. In addition to messenger RNA, both egg and sperm contain numerous kinds of noncoding RNAs that function as a vast regulatory system, controlling the extent to which messenger RNAs can be translated into proteins. Before EGA, development is controlled largely via the translation of messenger RNAs and the activity of noncoding RNAs inherited via the egg and sperm.

Epigenetics: Embryogenesis and Beyond

How, precisely, is transcription of DNA stopped before EGA and how is it restarted? The answer is the epigenome. There are many epigenetic processes, but the two most studied are histone modification and DNA methylation. Within chromosomes, DNA is combined with proteins called *histones* to form chromatin, a highly coiled and compact structure. Modifications to histones can change the structure of the chromatin causing it to wind more or less tightly, making the DNA more or less accessible to special proteins called *transcription factors*. Without being accessible to transcription factors, DNA transcription cannot occur. DNA methylation is the addition of a chemical compound to specific sites on the DNA molecule and acts as a physical barrier to transcription factors. In other words, both histone modification and DNA methylation, by regulating the extent to which regions of DNA (i.e., "genes") are accessible to transcription factors, can effectively turn genes on and off. It is hard to underestimate the significance of the epigenome. In fact, embryogenesis itself is an epigenetic process.

After fertilization the early embryo, the zygote, is in a state of totipotency, that is, the small number of cells of which it is initially composed can develop into any cell in the body (e.g., a heart cell, a neuron, a skin cell). Development is, in part, the differentiation of totipotent cells into specialized types of cells. In later development, these differentiated cells of the body (e.g., a heart cell, a neuron, a skin cell) are radically different in appearance and function despite the fact that they contain the same nuclear DNA. The epigenome is responsible for both totipotency and subsequent cellular differentiation. What differentiates a skin cell from a neuron is not differences in nuclear DNA (although, as we shall see, their nuclear DNA may in fact differ), but rather differences in their epigenomes. This means that in a skin cell and neuron different genes are turned on and off and hence, only certain genes can be transcribed in each type of cell. It is this difference in epigenetic "switches" or "markings" that leads to the radically different form and function of different types of cells.

Egg and sperm are both distinct types of cells. When their DNAs are joined in the zygote, their epigenetic markings are erased (with one important exception to be considered subsequently). This leads to totipotency, the ability of the cells of the early embryo to become any cells of the body. As development progresses, cells lose their totipotency as different epigenetic marks are established and become differentiated as specialized types of cells (e.g., a neuron or a skin cell). Differentiated cells will only give rise, through cellular division or mitosis, to cells of their own kind; for example, skin cells will only give rise to skin cells and heart cells to heart cells. This is a form of cellular inheritance. Hence, one definition of epigenetics is the study of heritable changes in gene transcribability and phenotype that occur without changes in DNA sequence.

While epigenetic modifications of the genome can be stable throughout the life course, such as the epigenetic modifications that contribute to cellular differentiation during embryogenesis, they can also be environmentally responsive, changing the transcribability of the genome in response to environmental inputs. The term *environmental epigenomics* reflects the constant interplay between the environment, which includes both endogenous (e.g., hormone levels or immune status) and exogenous (e.g., the perinatal environment) factors, and the epigenome. Consider several examples.

One exception to the initial erasure of epigenetic marks during embryogenesis concerns imprinted genes. Imprinting is an epigenetic phenomenon in which specific alleles are expressed in a parent of origin manner. In paternally imprinted genes, the paternal allele is epigenetically modified, preventing its transcription and leading to transcription solely from the maternal allele; in maternally imprinted genes, the maternal allele is epigenetically modified, preventing its transcription and leading to transcription solely from the paternal allele. The epigenetic marks of imprinted genes are maintained throughout embryogenesis. Abnormalities of imprinting can result in imprinting disorders.

One striking finding to emerge from the global rise of *in vitro* fertilization (IVF)—fertilization of an egg in a petri dish and implantation in the womb up to 6 days post fertilization—as a method of artificial reproduction is the rise of rare imprinting disorders among IVF-conceived children. Current estimates are that IVF children are approximately 514 times more likely to develop Beckwith–Wiedeman syndrome (BWS), a rare imprinting disorder, than non-IVF children, although the total numbers remain small owing to the rarity of the disorder (Hiura *et al*., 2012). Findings of an increased rate of analogous imprinting disorders in IVF animal models appear to rule out the possibility that this could be associated with subfertility. The reason for this increase in imprinting disorders is not known, but it could be due to any aspect of the IVF environment—the manipulation of egg and sperm,

the cultivation of the zygote in the suboptimal environment of a petri dish before implantation in the womb—disrupting the maintenance of epigenetic marks on imprinted genes.

It is well established that the prenatal environment can have a profound impact on developmental outcomes. The developmental origins of health and disease (DOHAD) is now an established area of medical research. Research in this field has demonstrated that factors such as maternal under- or overnutrition, or maternal levels of stress—factors often associated with the mother's socioeconomic status—can increase the risk of, for example, diabetes and obesity in children and diabetes, obesity, and cardiovascular disease in adults (Gluckman & Hanson, 2006). There is growing evidence that one of the mechanisms by which these environmental factors influence developmental outcomes is via environmentally induced changes to the epigenome (Lillycrop & Burdge, 2011). For example, there is evidence that maternal stress during pregnancy can reprogram the stress response of offspring with lifelong behavioral consequences (Mueller & Bale, 2008).

It is not only the prenatal environment that can reprogram the epigenome with significant developmental consequences. Mother rats that exhibit high-quality mothering (as measured by the amount of time they spend licking and grooming their pups) rear pups that, as adults, exhibit lower levels of stress as measured both physiologically and behaviorally, while pups raised by low-quality mothers exhibit, as adults, high levels of stress. Furthermore, female pups raised by high-quality mothers become, as adults, high-quality mothers themselves, while the females raised by low-quality mothers become low-quality mothers. Low-quality mothers also begin reproducing earlier and more frequently. Cross-fostering studies, in which pups are separated at birth from their biological mothers and raised by foster mothers, have consistently indicted that adult offspring are more likely to resemble their foster as opposed to biological mothers in stress-related responses and rearing behavior. These differences in rearing behavior have been associated with epigenetic changes in offspring in regions of the brain involved in both the stress response and maternal behavior (Weaver *et al.*, 2004).

Such environmentally induced epigenetic changes in gene transcribability and phenotype can serve an important adaptive function by enabling *phenotypic plasticity*. Phenotypic plasticity can be defined broadly as the ability of an organism to change phenotype in response to its environment. Modern evolutionary biology reflects the idea that adaptation is not limited to the process of natural selection (i.e., adaptation at the level of the species), but includes adaptation of the individual organism to its ecological niche. Adversity during perinatal development can forecast an increased level of demand in the environment the offspring will occupy.

Under such conditions, the animal's best interest is to enhance its behavioral (e.g., vigilance, fearfulness) and endocrine responsiveness to stress. These responses promote detection of potential threat, avoidance learning, and metabolic/cardiovascular responses that are essential under the increased demands of the stressor. Under high-risk conditions, when the probability of extended periods of growth and survival are low, the optimal strategy is to maximize the number of offspring through accelerated mating, increasing the chances that at least some offspring will survive to reproductive maturity. Such conditions favor a shift in reproductive investment toward quantity, while more favorable environmental conditions favor greater investment in individual offspring at the cost of mating, as offspring quality predicts successful competition for available resources and reproductive fitness.

Finally, there is a growing body of evidence that it is not only the epigenetic markings on imprinted genes that are not erased during embryogenesis. Specifically, there is evidence that environmentally induced changes to the epigenome can escape embryonic erasure and be transmitted intergenerationally. For example, studies have demonstrated that when a male rodent embryo is exposed in the womb to the endocrine disruptor vinclozolin (a common fungicide), it develops a phenotype characterized by defects in sperm production and subfertility. This defect has been associated with epigenetic changes at specific imprinted genes known to be involved in spermatogenesis. In the absence of any further exposure to vinclozolin, the phenotype can be transmitted from the exposed male to male offspring for up to three generations. In other words, an environmentally induced change to the epigenome and gene expression, and the resulting phenotype, can be transmitted intergenerationally without any change to the DNA sequence (Stouder & Paoloni-Giacobino, 2010). Decreases in human spermatogenesis are associated with imprinting defects on a number of the same genes that have shown abnormal epigenetic patterns in vinclozolin studies (Stouder & Paoloni-Giacobino, 2010). This is particularly suggestive given that in the past century a significant decline in sperm count has been documented in young, healthy males in industrialized countries, a finding that may in part explain a parallel decline in birthrates (Joffe, 2010). The rapidity of these changes strongly suggests that environmental factors play a role. Endocrine disruptors are a plausible contributing factor given their ubiquitousness in the environment in the form of herbicides, insecticides, and fungicides, resulting in daily exposure for many human populations.

ANEUPLOIDY

Epigenetic changes are changes that occur to DNA expression without any change to DNA content and sequence. Development, however, involves

changes to both. It is commonly assumed that each cell in the body contains two alleles (with a few exceptions) because each cell contains two chromosomes. Any departure from two chromosomes per cell (diploidy) is called *aneuploidy*. Errors of chromosomal replication are a normal part of embryogenesis, leading to a surprisingly high number of cells that exhibit one or another form of aneuploidy. Despite the association between aneuploidy and illness, there is a surprisingly high amount of chromosomal aneuploidy in the healthy adult brain. Recent conservative estimates place the overall percentage of aneuploid neural cells in the adult brain at an astonishing 10%, involving monosomy (1 chromosome), trisomy (3 chromosomes), tetrasomy (4 chromosomes), polyploidy (>4 chromosomes), and uniparental disomy (two copies of a chromosome from the same parent) (Rehen, 2005). Given an estimated 86 billion neurons in the adult brain, this yields a rough (conservative) estimate of 8.6 billion aneuploid neurons. Various lines of evidence indicate that brain tissues may be more prone to aneuploidy than other tissues. Mature aneuploid neurons are functionally active and integrated into brain circuitry. One likely result of this is neuronal signaling differences caused by altered gene transcription, as documented in mammalian neural cells. Thus, a network composed of intermixed diploid and aneuploid neurons might produce unique signaling properties.

Retrotransposons

One striking finding to emerge from the completion of the human genome-sequencing project is that approximately 48% of the genome is composed of transposable elements or "jumping genes" (Gibbs, 2003). Retrotransposons are a class of transposable DNA elements that move about the genome by a "copy and paste" mechanism known as *retrotransposition*. Retrotransposons first copy themselves to RNA, while the original DNA copy is maintained at the same location. The RNA copy is then "reverse-transcribed" into DNA and the DNA is inserted into the genome at a new location. Hence, these elements expand in number as they retrotranspose, leading to an increase in genomic DNA content and a change in DNA sequence and structure at the region of insertion. In so doing, they alter both the DNA sequence at the region of insertion and the total amount of DNA in the genomes in which they insert themselves. Because of their potential to disrupt genomic functioning by copying and pasting themselves throughout the genome in an uncontrolled manner, most transposable elements and retrotransposons are "turned off" by the epigenome. However, for a period during early embryogenesis retrotransposons are released from their epigenetic silencing. Why this occurs is not known, although the prevalence of retrotransposition in the brain has led to speculation that the

genetic diversity they create may in some way be related to the diversity of neurons (there are up to 10,000 different kinds of neurons in the normal adult brain) (Sciamanna, Vitullo, Curatolo, & Spadafora, 2009).

In addition to being activated during embryogenesis, retrotransposons are also active in those parts of the brain (the hippocampus and subventricular zone) that produce new neurons throughout life (Baillie *et al.*, 2011). The level of production of new neurons in the adult brain is positively and negatively modulated by environmental conditions, including environmental enrichment, stress, and aging. Exercise is known to have a significant impact upon hippocampal neurogenesis: it significantly increases the amount of brain-derived neurotropic factor (BDNF) in the hippocampus, a protein that supports the survival of existing neurons and encourages the growth and differentiation of new neurons and synapses (Gomez-Pinilla, Zhuang, Feng, Ying, & Fan, 2011). In mice, voluntary wheel running has been shown both to significantly increase neurogenesis in the brain and to double the amount of hippocampal retrotransposition (Muotri, Marchetto, Zhao, & Gage, 2009). What this entails is that the structure of the genome itself can change in response to environmental conditions. In humans, depending on its impact upon the brain, retrotransposon-induced DNA variability might induce behavioral changes that could help the individual adapt better to changing environments or, alternatively, increase the risk of neuropsychiatric disorders.

Telomeres and mtDNA

Telomeres are repeating DNA sequences bound by special protein complexes located at both ends of each of the (presumed) 46 chromosomes in the cells of the human body. They protect the base pairs at the ends of the chromosomes from deterioration and prevent them from fusing with neighboring chromosomes. Each time chromosomes are replicated in the process of cellular division, some of the telomere is lost (25–200 base pairs per division). When the telomere becomes too short, the chromosome reaches a critical length and can no longer replicate; this results in cell death. In highly proliferating cells such as germ and stem cells, telomere length is maintained by the enzyme telomerase, but in most cells of the body the activity of telomerase is low, and telomere length provides a marker for cellular aging. In recent years, shorter telomere length has been associated with a broad range of aging-related diseases, including many forms of cancer, stroke, vascular dementia, cardiovascular disease, obesity, osteoporosis, and diabetes. Telomeres of obese women have been found to be 240 base pairs shorter than those of lean women, and the telomeres of smokers are 18% shorter than nonsmokers (Valdes *et al.*, 2005). Shortened telomere length has also been associated

with an array of environmental stressors including chronic psychological stress (Chae *et al.*, 2014), and even with socioeconomic status in children aged 7–12 (Needham, Fernandez, Lin, Epel, & Blackburn, 2012).

Aging has been associated with a wide spectrum of alterations in mitochondria and mtDNA, including increased disorganization of mitochondrial structure, a decline in energy production, and accumulation of mtDNA mutations. The mitochondrial theory of aging proposes that progressive accumulation of mutations in mtDNA during a lifetime leads to an inevitable decline in mitochondrial function. The precise role of mtDNA mutation in aging remains uncertain, but their increase as part of the aging process is beyond doubt (Chistiakov, Sobenin, Revin, Orekhov, & Bobryshev, 2014).

CONCLUSION

Much of the effort to explicate the relationship between genotype and phenotype to date has been devoted to trying to find "predisposing" polymorphisms, gene variants that are risk factors for, or allow one to predict, complex phenotypes associated with both sickness [e.g., type 1 diabetes (T1D) or schizophrenia] and health (longevity, intelligence). While a few such polymorphisms have been identified (e.g., the BRCA1 and 2 genes are associated with an increased risk of genetic breast and uterine cancer), their identification has been largely unsuccessful. For disorders, such as T1D, which have been associated with many different polymorphisms—in the case of T1D, 60 and counting, only a small number of genetically susceptible individuals progress to clinical disease, and heritability estimates for T1D are relatively low (Knip *et al.*, 2012). In other words, the polymorphisms lack predictive value, indicating that the disease is the result of some form of complex biological predisposition interacting in complex ways with as yet unknown environmental triggers. Adding to the complexity is the fact that more than one protein can be transcribed from the same gene.

Given that there are estimated to be more than 100,000 proteins in the human body—and the number may be significantly higher—yet approximately 20,000 genes in the human genome, necessitates a rethinking of the assumption that each gene contains the 'instructions' for making just one protein. AS (alternative splicing) allows a single gene to produce multiple transcripts. AS occurs when newly transcribed RNA (known as pre-mRNA) is rearranged by processes in the cellular environment. This results in different mRNAs and different proteins, called isoforms (Nilsen & Graveley, 2010). AS is estimated to occur in 95% of human genes, and can result in numerous proteins being synthesised from the same gene (e.g., the neurexin proteins are encoded by three genes, but it is estimated that more than 1000

neurexin isoforms are produced by extensive AS). Isoforms of the same gene can exert radically different and even opposed physiological effects.

From a life-course perspective on the genotype–phenotype relationship, the failure to find predisposing genes for most complex human traits is not at all surprising: Genes are not the sole biological agent of inheritance; as a result of chance errors in replication and the activity of retrotransposons during the developmental process, persons do not have one genome, but different genomes in different cells in their bodies; the epigenome, which is a key to the entire process of development from conception on, can be highly environmentally responsive and can reprogram gene expressivity in enduring ways in response to environmental inputs; the environment changes not only gene expressivity, but the genome (or genomes) itself, through processes such as retrotransposition, the shortening of telomeres, and mutations in mtDNA. These changes are associated with the life course—telomere shortening and mutation accumulation in mtDNA are part of the aging process—and are influenced by the environments the individual occupies throughout her life: Telomere length has been associated in children and adults with stressful environments (such as environments characterized by low socioeconomic status); retrotransposition continues throughout life in certain brain regions and is associated, via increased neurogenesis, with environmental inputs such as environmental stimulation and exercise.

The problem with the search for genes "for," or genes "predisposing for" complex phenotypes is that first, it unscientifically privileges genes as the sole biological agent of inheritance, ignoring all of the other inherited biological elements in the absence of which genes would have no effect whatsoever. It is well to keep in mind, particularly regarding the search for genes involved in, for example, intelligence, that *humans possess fewer protein-coding genes than corn*. One of the surprising findings of the Genome Project was that the human genome contains an estimated 20,000 protein-coding genes, less than maize (i.e., corn), which contains over 32,000 protein-coding genes, and close in number to the nematode, with approximately 19,000. And many genes appear to be preserved across species. Surely, the distinctive properties of the human brain and human behavior are the result of something other than what we have less of than corn. Second, this search is based on a static conception of the genome, ignoring the manifold transformations it undergoes as part of its, and our, life course. And third, it presupposes the anachronistic dichotomy between "nature" and "nurture," "genes," and "environment." Is chromatin, for example, in which the DNA is wrapped and which allows genes to be transcribed by changing its configuration in response to environmental inputs, "genes" or "environment"? When the configuration of genes changes in response to environmental inputs, does the environment "become" genes? The life-course approach shows us that such

simplistic dichotomies belie the complexity, fluidity, and temporality of the biological world.

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