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GHOST IN YOUR GENES

ASK THE EXPERT

Randy Jirtle answered viewer questions about epigenetics on August 2 and November 1, 2007 (see below). Please note we are no longer accepting questions, but for more information, please go to [Epigenetic Therapy, A Tale of Two Mice](#), and [Links & Books](#).

FROM AUGUST 2, 2007

Q: Scientists have already proved (or at least demonstrated) epigenetic inheritance in plants and mice. How difficult do you think such inheritance will be to demonstrate in humans?

Israel Barrantes, Madison, Wisconsin

A: There is already evidence that epigenetic transgenerational inheritance can also occur in humans in response to food supply and smoking (Pembrey *et al.*, *Eur. J. Hum. Genet.* 14: 159-166, 2006). Nevertheless, until the epigenetically changeable targets in humans are defined, it will not be possible to determine if such associations are directly mediated by epigenetic changes, as we were able to demonstrate in the viable yellow agouti (A^{vy}) mouse (Waterland and Jirtle, *Mol. Cell. Biol.* 23: 5293-5300, 2003). With the rapid development of new methods to define genome-wide epigenetic variations in humans, I believe the importance of epigenetic alterations in the transgenerational inheritance of human health and disease will occur quite swiftly.

Q: In the online audio presentation, Dr. Dana Dolinoy states that the epigenome is responsible for determination of cell type and activity. Does the bisphenol A finding suggest that fetal or environmental exposure to plastics could play a direct role in a genetic propensity toward obesity in humans?

Chantel Smith, Toronto, Canada

Q: Could there be a connection between the increase in plastics in our environment and rising obesity rates?

Randy Grenier, Waltham, Massachusetts

A: We have recently demonstrated that exposure of pregnant mice to bisphenol A (BPA), a building block of polycarbonate plastics and epoxy resins used to make consumer items ranging from water bottles to dental sealants, significantly reduces DNA methylation in A^{vy} mice (Dolinoy *et al.*, *Proc. Natl. Acad. Sci. USA* 104: 13056-13061, 2007). This results in the birth of more yellow offspring, mice that become obese and have a higher incidence of diabetes and cancer as adults. Thus, there could be a connection between the increase in plastics in our environment and the rising incidence of obesity in humans. However, such an association will not be able to be demonstrated unequivocally until the expression and function of genes involved in human obesity are shown to be altered by BPA.

[Editor's note: For more on the agouti mice, see [A Tale of Two Mice](#).]

ENLARGE



Randy Jirtle is director of the Laboratory of Epigenetics and Imprinting at Duke University and is a professor of radiation oncology at the school's medical center. His groundbreaking research with agouti mice has revealed that a mother's diet during pregnancy can influence gene expression in her offspring by altering the epigenome. Since obtaining his M.S. (1973) and Ph.D. (1976) in radiation biology from the University of Wisconsin-Madison, Jirtle has published over 150 scholarly articles and registered three patents. He currently serves on the editorial boards of three scientific journals and manages the epigenetics Web site [geneimprint.org](#), which focuses on the quest to understand how environmental factors can affect human disease.

GHOST IN YOUR GENES


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Q: If BPA has the same effect on humans as it did the mice in your study, why aren't all human babies born sick and obese?

Anonymous

A: BPA exposure during pregnancy increases the incidence of yellow offspring, but it does not result in all of the offspring having a yellow coat color and becoming obese. Therefore, if BPA has the same effect on humans as it does in mice, it would simply increase the percentage of humans who become obese as the BPA exposure increases. This happens to be the situation found in Western cultures, regardless of whether BPA is the culprit.

Q: How do the exposure levels of BPA in the agouti mice experiments compare to human exposure levels—especially exposure levels in pregnant women?

Dr. Gloria Jahnke, Chapel Hill, North Carolina

A: It is difficult to compare the BPA dose used in our mouse study with that to which humans are exposed, because in humans, the BPA is found in the plasma or excreted in the urine. We can't tell exactly how much of the chemical people ingest. The level of BPA that the pregnant mice were exposed to in our study was five times lower than the maximum nontoxic threshold dose in rodents (Dolinoy *et al.*, Proc. Natl. Acad. Sci. USA 104: 13056-13061, 2007). Although this is likely higher than typical human exposure, it produced no significant effects on reproductive outcomes, litter size, or offspring health at birth. It did, however, markedly increase the incidence of mice born with a yellow coat color—animals that become obese and have higher incidences of diabetes and cancer as adults.

Q: If environmental factors can influence the gene expression in offspring, can that process be reversed or altered by other factors (diet, drugs, gene therapy, etc.) after the offspring are born?

Vladimir Sanchez, San Francisco, California

A: We have shown that during early fetal development, maternal nutrient supplements of methyl-donating substances (folic acid, choline, vitamin B12, and betaine) or genistein, found in soy products, can counteract the reduction in DNA methylation caused by BPA. Nevertheless, we have not yet tested if exposure to these nutrient supplements can reverse the negative effects of BPA in adulthood.

Weaver *et al.* (Nat. Neurosci. 7: 847-854, 2004) at McGill University, however, have shown recently that maternal nurturing behavior can stably alter the epigenotype in rat pups soon after birth. Moreover, these epigenetic changes are reversible in adulthood following methionine supplementation or treatment with histone deacetylase (HDAC) inhibitors (Weaver *et al.* Proc. Natl. Acad. Sci. USA 103: 3480-3485, 2006). Thus, data supporting the reversal of environmentally induced epigenetic changes via dietary supplementation or pharmaceutical therapy in adulthood is mounting.

Q: I don't see how twins demonstrate epigenetic changes as they differ with age. Aren't there other factors at play that have nothing to do with the epigenome?

Anonymous

A: If twins split from a single egg were absolutely identical, both the genome (DNA sequence) and epigenome (DNA methylation, histone marks, etc.) would be exactly the same. This is not, however, what is observed (Fraga *et al.*, Proc. Natl. Acad. Sci. USA 102: 10604-10609, 2005). Although the epigenomes are similar in young twins, they are increasingly different in older twins, especially if the twins have lived in different environments and have had different social habits (e.g., smoking, drinking, and eating). Interestingly, identical twins can also vary in their susceptibilities to diseases and their physical and behavioral characteristics. Although there are several possible

explanations for these observed differences, one is the existence of differing epigenomes.

Q: In our physiology and anatomy class, we discussed HIV and AIDS, and we talked a little about how there are a few people who are naturally immune to the virus. Could medications aimed at altering the epigenome provide similar protection?

Students at Mt. Eden High School, Hayward, California

A: I am not an HIV/AIDS researcher, but if the cellular pathways involved in "natural immunity" to HIV have been delineated, it may be possible to alter them appropriately by targeting the epigenome.

Q: Have scientists found environmental factors that may influence people to develop diseases like MS or ALS?

Maureen Garrity, Helena, Montana

A: Presently, it is unknown whether environmentally induced epigenetic changes in gene regulation are involved in the formation of MS (Multiple Sclerosis) or ALS (Amyotrophic Lateral Sclerosis or Lou Gehrig's Disease). However, if scientists discovered such a connection, it could result in novel ways not only to treat but also to potentially prevent these diseases.

Q: It sounded from the show as if epigenetics is quite successful in treating life-threatening diseases. Which hospitals are using epigenetic therapies, and are trials still going on? Also, how does one qualify for the treatment? If it's this successful, why aren't we treating all cancer patients this way?

Debra Carte, North Muskegon, Michigan

Q: What's the future of epigenetic therapy in humans?

Anonymous

A: The future of epigenetic therapy is promising, particularly in the treatment of some cancers. Drugs that inhibit the DNA methyltransferases, which place methyl groups on the DNA, are now approved for clinical use in the United States for the treatment of certain cancers. This has ushered in a new era of cancer treatment involving epigenetic therapy. (For reviews see: Issa, J.P., *Clin. Cancer Res.* 13: 1634-1637, 2007; Yoo, C.B., & Jones, P.A., *Nat. Rev. Drug Discov.* 5: 37-50, 2006).

Epigenetic therapies may also be useful in the treatment of neurological disorders. There is evidence that the histone deacetylase (HDAC) inhibitor, valproic acid, increases the effectiveness of anti-psychotic medications in the treatment of schizophrenia and bipolar disorder. (For review see: Citrome, L. *Psychopharmacol. Bull.* 37 (Suppl 2): 74-88, 2003.)

Like all new therapies, it will take time to determine the diseases that respond best to epigenetic therapy, and for optimal drugs to be discovered. Please contact your personal physician for more specific information on epigenetic therapy.

Q: Are allergies epigenetic?

Chantel Smith, Toronto, Canada

A: It is presently unknown if epigenetic changes are directly involved in the development of allergies or asthma; however, this possibility is now being investigated actively. (For review see: Vercelli, D., *J. Allergy Clin. Immunol.* 113: 381-386, 2004.)

Q: Before my wife and I had our child, I read a few studies on epigenetics, concentrating on studies dealing with dietary methyl donors. We both took supplements before trying to get pregnant, and

we both continued to take them while pregnant. When my daughter was born, she came out with blond hair and blue eyes, nothing like ours. All of her teachers have said that she learns extremely quickly compared to others and has a fantastic memory. Could our consuming simple nutrients have provided such physical and intellectual attributes?

Britt E., Little Rock, Arkansas

Q: Can a person manipulate his or her environment in such a way as to maximize his or her IQ and minimize his or her genetic disposition for mental illness? Also, have scientists been able to reverse a negative gene expression brought on by epigenetics such as the one expressed in the twin mice?

Anonymous

A: Choline supplementation during pregnancy in rats increases learning ability, enhances synaptic function, and offers protection from neurotoxicity (Li, Q., *J. Neurophysiol.* 91: 1545-1555, 2004). These effects of choline on neurological function most likely involve altered gene expression and associated changes in nerve cell growth and differentiation mediated by epigenetic changes, such as DNA methylation. Although the animal data on choline and hippocampal development are compelling, studies are needed to determine whether choline supplementation during pregnancy has the same effect in humans. (For review see: Zeisel, S.H., *J. Pediatr.* 149 [Suppl. 5]: S131-5136, 2006.) It is unknown if food supplements or epigenetic drug therapy in adulthood can reverse an epigenetically regulated negative effect on neural function in humans.

Q: Is there any evidence that mental activity, as opposed to nutrition or exposure to environmental hazards, affects children? Is, say, the child of a chess player likely to be better at chess than someone who does not play?

Steven Meyer, Melbourne, Australia

Q: The discredited Russian geneticist Trofim Lysenko claimed to have discovered that acquired characteristics could be inherited. Is it possible that he may in fact have discovered some phenomena (behind all his false science) that were true after all?

Paul Sinclair, Austin, Texas

A: The chess player scenario is another example of the French biologist Jean-Baptiste Lamarck's theory of the inheritance of acquired characteristics where individuals are proposed to inherit the traits of their ancestors. For example, this theory proposes that giraffes have long necks because they were gradually lengthened by stretching to eat leaves high up in trees—an adaptive trait then inherited by their offspring. It also claims that sons of blacksmiths have well-developed arm muscles because their fathers strengthened those muscles through their work. The theory of Lamarckism was revived in the Soviet Union during the 1930s by agronomist Trofim Lysenko, because it was compatible with Stalin's ideological opposition to genetics.

Epigenetic regulation of genes acquired during early development is inherited not only during cell division (mitotic inheritance), but it also can be passed on from one generation to the next (meiotic inheritance). (For review see: Whitelaw, N.C., & Whitelaw, E., *Hum. Mol. Genet.* 15 (Spec. No 2): R131-R137, 2006.) Nevertheless, there is no evidence that enhanced human parental mental activity in adulthood increases the mental acuity of their children through the inheritance of acquired epigenetic traits. It remains to be seen if additional epigenetic research elevates Lamarck's stature in the field of evolution.

Q: How long do scientists think it takes for a given environmental factor or factors—for instance, heavy smoking or overeating—to alter someone's epigenetic profile?

Weiniu Gan, Maryland

A: We have shown that the amount of DNA methylation at the *Agouti* locus varies greatly between individual A^{vy} mice. In contrast, there is no significant

variation in DNA methylation between tissues within an animal. This indicates that the DNA methylation marks controlling agouti gene expression were established in the early embryonic stem cells probably before the developing embryo implanted in the womb (Waterland and Jirtle, *Mol. Cell. Biol.* 23: 5293-5300, 2003). Other windows of susceptibility to environmentally induced epigenetic alterations may be longer, such as early childhood development and puberty. Once these epigenetic marks are established, however, the effects on the individual remain throughout life, and can even potentially be passed on to future generations through the egg and the sperm.

Q: Lions feed on meat and are faster and stronger than goats, which eat grass. Humans eat almost everything and are on the top of the evolutionary tree. I was wondering if there was an association between food intake and species evolution over millions of years. What do scientists think?

Ping, China

Q: With the discovery of epigenetics, it seems that behavior can influence the activation and deactivation of the genetic code that can even be passed on to the next generation. Does this mean it is possible that human culture can influence the evolutionary process?

Kenneth Humphrey, El Paso, Texas

A: Mammals whose offspring are born rather than hatched from an egg (marsupial or placental mammals) have imprinted genes. Imprinted genes are expressed from only one parental copy in a parent-of-origin dependent manner (Jirtle, R.L., & Weidman, J.R., *Am. Sci.* 95: 143-149, 2007). The parent-specific non-functional copy is silenced epigenetically. Moreover, imprinting can be altered after birth by diet (Waterland, R.A., et al., *Hum. Mol. Genet.* 15: 705-716, 2006). It has been postulated that disruption of genomic imprinting may contribute to mammalian speciation (Vrana, P.B., *Nat. Genet.* 20: 362-365, 1998). Thus, environmental factors including diet could be involved in the evolution of placental mammals by altering the repertoire of imprinted genes; however, there is presently no direct evidence of this occurring.

Q: There has been much alarming research linking several chemicals to negative genetic and epigenetic changes in the womb. How do we translate this into policy, hopefully preventing harm to future generations across the board? And how do we decide which chemicals to rally against?

Jill McElheney, Winterville, Georgia

A: We have demonstrated recently that when female pregnant mice are exposed to BPA, the incidence of yellow A^y offspring is markedly increased because DNA methylation of the agouti gene is decreased (Dolinoy *et al.*, *Proc. Natl. Acad. Sci. USA* 104: 13056-13061, 2007). BPA also epigenetically alters gene expression of at least one other gene, indicating a genome-wide effect. Yellow agouti mice become obese in adulthood and have a high probability of developing diabetes and cancer. Consequently, BPA exposure leads to adult diseases in agouti mice by altering the epigenome during the earliest stages of development—a condition that can be counteracted by maternal nutrient supplementation with methyl-donating substances (folic acid, etc.) or genistein.

The ability to extrapolate our agouti mouse results to humans, however, is not straightforward because the repertoire of epigenetically regulated disease susceptibility genes varies between species. (For review see: Jirtle, R.L., & Skinner, M.K. *Nat. Rev. Genet.* 8: 253-562, 2007.) The ability to identify human epigenetically regulated disease susceptibility genes in a genome-wide manner will improve rapidly, in part, because the [NIH Epigenetics Roadmap Initiative](#) was approved this year for immediate implementation as a five-year program. Thus, this limitation should become less problematic in the future, thereby improving human risk assessment for physical and chemical agents that potentially are harmful because of their ability to alter the epigenome, rather than mutate the genome.

Current risk-assessment procedures for evaluating the potential health effects of environmental exposures do not explicitly address epigenetic changes. It is also important that other endocrine-disrupting agents like BPA be assessed for their ability to epigenetically alter gene expression during early development because this is the stage of life when cellular function is most vulnerable to epigenetically active environmental factors.

Thus, based on our findings and those of other scientists, it seems prudent at this time for women, who are or plan to get pregnant, to limit their exposure to BPA. Finally, it is important to stress that although methyl-donating substances or genistein can counteract the negative effects of BPA on the epigenome, high concentrations of these food supplements could also be harmful. While a glass of wine at dinner may be good for your heart, a gallon surely isn't!

Q: I find the influence of lifestyle and diet on genetics fascinating. What foods and lifestyle changes do you recommend as a family conceives and raises children?

Jennifer, Massillon, Ohio

Q: What is the single most important food we can add to or increase in our diet that will help us remain thin?

Patricia Frank, Morristown, New Jersey

Q: Have you changed your diet based on your studies, for example, do you eat more soy products? If you have changed your diet, can you provide details? Thank you for the fascinating program.

Jane, Seattle, Washington

Q: My wife is pregnant and craves lemon salt. She eats a lot of it and also eats sour candy. Could that stuff be bad for the baby?

Dan M., San Antonio, Texas

Q: My wife and I had a daughter with multiple genetic deformities who died at just a week old. Could the drugs I did in and after high school—marijuana and LSD to be specific—have caused my daughter's problems?

Anonymous

A: These questions cannot be answered because of the present lack of knowledge about the impact of diet and lifestyle on the human epigenome and the formation of human complex diseases.

My mother told me repeatedly when I was a kid to eat my vegetables and make sure I always ate breakfast. This seems to me to still be sound advice.

FROM NOVEMBER 1, 2007

Q: The analysis by Pembrey and Bygren indicated that the effects of nutrition are most commonly observed in the grandchildren of men who were malnourished in late childhood and women who were malnourished in utero. Is there an explanation as to why the effect is observed in the grandchildren more often than in the children?

Glen and Joanne Fox, Colorado Springs, Colorado

Q: The Swedish researchers seemed to be saying that grandfathers who experienced famine at the time of puberty had male grandchildren who lived longer. On the other hand, women who experienced famine in utero had female grandchildren who lived shorter lives. Is this correct? How do you explain the difference? Why would the grandchildren of affected men have longer lives?

Paul Shoaps, Tampa, Florida

A: The reasons for these intriguing findings are unknown. Presently, it is not even clear if these associations result from alterations in the epigenome. As we identify more genes involved in chronic diseases like diabetes and obesity,

the mechanisms for these fascinating transgenerational inheritance patterns will become more evident.

Q: If my grandparents suffered through the Great Depression, would some kind of epigenetic change be present in me?

Robert Logan, Fort Worth, Texas

A: Not necessarily! The ability of environmental conditions to cause epigenetic changes varies with time during our life, and also with the amount of exposure at these vulnerable periods of time. Consequently, it is not possible presently to know whether the suffering of your grandparents during the Depression resulted in an epigenetic legacy in your genome.

Q: Is it possible that epigenetics play a role in animal instinct, causing behaviors that don't have immediately apparent rewards? I'm thinking about things along the lines of salmon swimming upstream to spawn and then dying.

Steve Boucher

A: It is possible that at critical times during early development the brain in salmon is epigenetically programmed by environmental conditions, and that this results in an adulthood behavior like swimming upstream of a specific river to spawn. This would be comparable to the epigenetic programming of nurturing behavior in the brains of rat pups by maternal licking and grooming after birth (Szyf et al., *Reprod. Toxicol.* 24: 9-19, 2007). More research will have to be done, however, to determine if salmon spawning behavior involves "epigenetic memory."

Q: Are there epigenetic implications for the theory of evolution?

Mike Thron, Folsom, California

A: Genetic machinery evolved about 150 to 200 million years ago to epigenetically inactivate the expression of a gene in a parent-of-origin dependent manner in Therian "live-bearing" mammals (Killian et al., *Mol. Cell* 5: 707-716, 2000). The phenomenon of genomic imprinting results in monoallelic expression of genes that is dependent on stage of development, tissue type, and species (Jirtle and Weidman, *Am. Sci.* 95: 143-149, 2007). There is accumulating evidence that the imprinting of genes is involved in mammalian speciation (Hunter, *EMBO Rep.* 8: 441-443, 2007). Consequently, the epigenetic dysregulation of this subset of genes would be expected to play a critical role in the formation of human diseases and neurological disorders.

Q: Some schools of thought in psychology have suggested that we operate bio-psychosocially by having gene expression or behavioral predispositions determined by the idea of nature via nurture or a diathesis-stress model. Can our emotions change how our bodies operate epigenetically? Can stress cause sickness?

Jeff Giblin, Vancouver, British Columbia, Canada

Q: Can a person's state of mind lead to epigenetic changes in how genes are expressed? Can we "think" ourselves into being sick or well?

Jeff Deutsche, Grand Summit, Pennsylvania

Q: I see how diet and habits such as smoking could affect our epigenome, but has any research been done on humans or lab mice on how our moods might affect epigenetics? Does a healthy body rely upon positive thinking?

Sarah Alexander, Graton, California

A: Fear conditioning in the rat results in brain DNA methylation coupled with the silencing of the memory suppressor gene, *PP1* (*Protein phosphatase 1*), and DNA demethylation and activation of the synaptic plasticity gene, *RELN* (*Reelin*) (Miller and Sweatt, *Neuron* 53: 857-869, 2007). It is presently

unknown whether similar molecular changes occur in humans in response to mood-altering stimuli. Nevertheless, it is clear that understanding the role of epigenetics in mediating neural function will be essential to fully understanding the molecular processes by which memory formation and human cognition are altered by stimuli from both outside and inside of the brain.

Q: I recently read an article on autism that gave the following analogy: "Where genes load the gun, the environment pulls the trigger." This sounds a lot like what I heard about epigenetics on the NOVA program this evening. The number of children diagnosed with autism spectrum disorder (ASD) has increased tenfold in the past 20 years. As a teacher working with this increasing student population, I would like to know if there are any diet and/or environmental "heads ups" that could be given to prospective parents or help to ameliorate the condition in children already struggling with ASD. Thank you.

Anita Holmes, North Pole, Alaska

A: To my knowledge, there are presently no known dietary substances or environmental agents that prevent or alleviate the symptoms of ASD by altering the epigenome. We will only be able to systematically determine preventative/therapeutic agents once we have identified genes involved in autism whose epigenetic deregulation is shown to be mechanistically involved in the formation of this neurological disorder.

Q: Are there standard blood tests that can be done or signs that can determine if Myelodysplastic Syndromes (MDS) is present or if a person is at risk for MDS? Will family doctors be able to identify epigenetic problems and prescribe epigenetic therapy?

Karen, Alfred, Maine

A: I am not a physician, so I do not know the answer to this question. I would contact Dr. Jean-Pierre Issa (see [Epigenetic Therapy](#) elsewhere on this site), since he is treating MDS patients with epigenetic therapy.

Q: I'd like to know if you have any idea of what would happen if we injected somebody with a drug that would erase all the epigenetic tags that control the on and off switching of genes.

Arnel, Roanoke, Virginia

A: There are a number methyltransferase (DNMT) proteins involved in new and maintenance DNA methylation. When *Dnmt3a* is absent only from the nervous system of mice, neuromuscular defects and lifespan shortening are observed (Nguyen et al., *Dev, Dyn*. 236: 1663-1676, 2007). Mouse embryos lacking *Dnmt3a* in all cells in the body are born small and die about a month after birth, while those without *Dnmt3b* do not develop past mid-pregnancy. Mice without both *Dnmt3a* and *Dnmt3b* are unable to survive much past fertilization (Okano et al., *Cell* 99: 247 1999). Mice deficient for *Dnmt1* lose most of their DNA methylation and also die early in embryogenesis (Li et al., *Cell* 69: 915-926, 1992). Moreover, mutations in the human *DNMT3B* are found in ICF syndrome, which is an autosomal recessive disease characterized by reduced DNA methylation, variable immunodeficiency, centromeric instability, and facial abnormalities. Thus, eliminating DNA methylation genome-wide is not compatible with life.

Q: My niece Bridget, who is autistic, was featured on this episode. Is there a possibility of one day injecting humans with something that could in essence turn off and on a "mised" gene so to speak, if one exists, and possibly offer a cure for autism or other ailments? Or is a person's fate decided in the womb?

Alice Gould, Philadelphia, Pennsylvania

A: Presently, it is not possible to answer your question because we do not know the gene whose function is altered either genetically and/or

epigenetically in Bridget. However, if the cause of her autism is due to an epigenetic change rather than a random mutation in a gene, then it may be possible in the future to ameliorate the autistic symptoms with the use of an agent that normalizes the regulation of the epigenetically dysregulated gene.

Q: My son was diagnosed with the eye disorder Familial Exudative Vitreoretinopathy when he was four years old. Understanding that this condition is hereditary and there is no known history of this disease on either side of the family, could this condition have potentially been caused by epigenetic factors?

Sue, Atlanta, Georgia

A: It is possible that the expression of a gene mechanistically involved in FEVR (Familial Exudative Vitreoretinopathy) was inappropriately shut down by an epigenetic mechanism during early development; alternatively, a spontaneous DNA mutation may have occurred in a gene involved in this disease. Until the gene that resulted in FEVR in your son is identified, it will not be possible to discriminate between these two possibilities.

Q: How is it possible that one twin can be affected by diseases with epigenetic links while the other is not?

Joseph S. Garcia, Chicago, Illinois

A: When there are two babies developing in the same womb, the supply of nutrients, exposure to environmental toxicants, etc. may not be the same because their blood supplies will most likely not be identical. As we showed with the Agouti mice (Jirtle and Skinner, *Nat. Rev. Genet.* 8: 253-262, 2007), even subtle changes in maternal nutrition can dramatically change the coat color of the offspring and their susceptibility to diseases like obesity, diabetes, and cancer by simply by altering the epigenome.

Q: I have two boys who were born in Korea to different mothers. They are not related at all, but they both have autism and an almost identical list of allergies. I have two questions/comments. Could this have been caused by stress from their having moved from foster home to foster home to here? Or could this have something to do with the Korean War? I know there is speculation with Vietnam and Agent Orange, but what about other wars?

Cheryl, Visalia, California

A: Rat studies show that maternal nurturing of the offspring after birth reduces their response to stress by altering the epigenome in the brain (Szyf et al., *Reprod. Toxicol.* 24: 9-19, 2007). There is also evidence in humans that prenatal exposure to maternal stress induced by war can increase the risk of subsequently developing schizophrenia (van Os, et al., *Br. J. Psychiatry* 172: 324-326, 1998). Nevertheless, until the genes involved in autism are defined, it will not be possible to determine if environmental factors like stress from war or the lack of a stable home during childhood can result in their epigenetic dysregulation.

Q: As a college student who is currently applying to medical school, what implications could epigenetics have on disease treatment and prevention? Do you see traditional medicine changing and being replaced with a more genetic basis?

Jake Kenyon, Lawrence, Kansas

A: The important role that epigenetics plays in human diseases and neurological disorders should be appreciated to a greater extent by the time you are a practicing physician. Already epigenetic therapeutic approaches, involving DNA methylation inhibition and histone deacetylase inhibition, are being used to treat cancer (Yoo and Jones, *Nat. Rev. Drug Discov.* 5: 37-50, 2006). Epigenetic therapies are also undergoing increased development to directly target sites in the genome, including the directed silencing of specific oncogenes via DNA methylation (Hoffman and Hu, *Cell Mol. Neurobiol.* 26:

425-438, 2006). Therefore, you should have more agents that target specific regions of the epigenome for the prevention and treatment of human diseases and disorders than are now available. However, to successfully utilize these novel drugs, you will need a good working knowledge of epigenetics, nutrition, and toxicology.

Q: There is a long-standing debate as to whether the cause of homosexuality is genetic or environmental. This epigenetic theory seems to me to explain that confusion. I have known twins who were of opposite sexualities. Could it be that epigenetic factors determine sexual orientation? And is anyone studying this?

Douglas Copp, Toronto, Ontario, Canada

A: Epigenetic variations are known to result in markedly different phenotypes in genetically identical animals (Jirtle and Skinner, *Nat. Rev. Genet.* 8: 253-262, 2007). Thus, it is reasonable to expect that humans may also vary in their behaviors because of epigenetic, in addition to genetic, differences.

CONCLUDING REMARKS FROM DR. JIRTLE

Human epidemiological and animal experimental data indicate that the risk of developing adult-onset diseases is influenced by persistent adaptations to prenatal and early postnatal exposure to environmental factors. Moreover, the link between what we are exposed to during pregnancy and disease formation in adulthood appears to involve epigenetic modifications like DNA methylation. Therefore, to gain a clearer understanding of human disease formation, genes whose function is particularly sensitive to environmentally induced epigenetic modification need to be identified.

Genomic imprinting is an epigenetic form of gene regulation that results in monoallelic, parent-of-origin dependent gene expression (Jirtle and Weidman, *Am. Sci.* 95: 143-149, 2007). The functional haploid state of imprinted genes makes them susceptibility loci for diseases since a single genetic or epigenetic mutation can alter their function.

We have recently developed a computer-learning algorithm that identified 600 candidate-imprinted genes in the mouse (Luedi et al., *Genome Res.* 15: 875-884, 2005). Interestingly, we have predicted humans not only have fewer imprinted genes, but also that the repertoire differs greatly from that in the mouse (Luedi et al., *Genome Res.* 17: December, 2007). By mapping the human imprinted gene candidates onto the landscape of disease risk defined by linkage analysis, we are now poised to determine the importance of imprinting in the etiology of complex human diseases and neurological disorders. Ultimately, such studies should finally allow many of the important questions asked, but not discussed above, to be answered. ■

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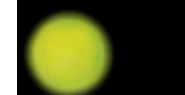
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