A PATCHWORK MIND

We each have two parents, but their genetic contributions to what makes us *us* are uneven. New research shows we are an amalgam of influences from Mom and Dad

By Melinda Wenner

Your memories of high school biology class may be a bit hazy nowadays, but there are probably a few things you haven't forgotten. Like the fact that you are a composite of your parents—your mother and father each provided you with half your genes, and each parent's contribution was equal. Gregor Mendel, often called the father of modern genetics, came up with this concept in the late 19th century, and it has been the basis for our understanding of genetics ever since.

But in the past couple of decades, scientists have learned that Mendel's understanding was incomplete. It is true that children inherit 23 chromosomes from their mother and 23 complementary chromosomes from their father. But it turns out that genes from Mom and Dad do not always exert the same level of influence on the developing fetus. Sometimes it matters which parent you inherit a gene from—the genes in these cases, called imprinted genes because they carry an extra molecule like a stamp, add a whole new level of complexity to Mendelian inheritance. These molecular imprints

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silence genes; certain imprinted genes are silenced by the mother, whereas others are silenced by the father, and the result is the delicate balance of gene activation that usually produces a healthy baby.

When that balance is upset, however, big problems can arise. Because most of these stamped genes influence the brain, major imprinting errors can manifest themselves as rare developmental disorders, such as Prader-Willi syndrome, which is characterized by mild mental retardation and hormonal imbalances that lead to obesity. And recently scientists have started to suspect that more subtle imprinting errors could lead to common mental illnesses such as autism, schizophrenia and Alzheimer's disease. A better understanding of how imprinting goes awry could provide doctors with new ways to treat or perhaps even prevent some of these disorders.

Through the study of imprinted genes, researchers are also uncovering clues about how our parents' genes influence our brain—it seems that maternal genes play a more important role in the formation of some brain areas, such as those for language and complex thought, and paternal genes have more influence in regions involved in growing, eating and mating. "You need both Mom and Dad in order to get a normal brain," says Janine LaSalle, a medical microbiologist at the University of California, Davis, whose lab focuses on imprinting. "We're really at the beginning of understanding what that means."

To understand the implications of imprinting, it helps to know a few basics. Imprinting is an epigenetic (meaning "beyond genetic") mechanism, a molecular change that can happen within a cell that affects the degree to which genes are activated, without changing the underlying genetic code. The type of imprinting that happens in egg and sperm cells is known as "genomic imprinting," a reference to its fundamental heritable nature. Other types of imprinting can happen as a result of environmental influences, such as parental nurturing or abuse. [For more on epigenetics, see "The New Genetics of Mental Illness," by Edmund S. Higgins; Scientific American Mind, June/July 2008.]

As recently as a few decades ago, very few people imagined that heritable genetic influences existed beyond the basic genetic code in our DNA. Then, in 1984, biologists at the University of Cambridge and at the Wistar Institute in Philadelphia separately tried to breed mice that had either two copies of a father's chromosomes or two copies of a mother's chromosomes, instead of one copy from each parent. According to Mendelian theory, the baby mice should have been fine—after all, they had the correct number of genes and chromosomes. All the fetuses died, however, suggesting that simply having two of each chromosome is not sufficient—each pair must be made up of one chromosome from Mom and one from Dad. But the researchers did not yet know why.

(Sperm cells **silence some genes** with molecular imprints, and egg cells silence others.)

FAST FACTS
Genetic Complications

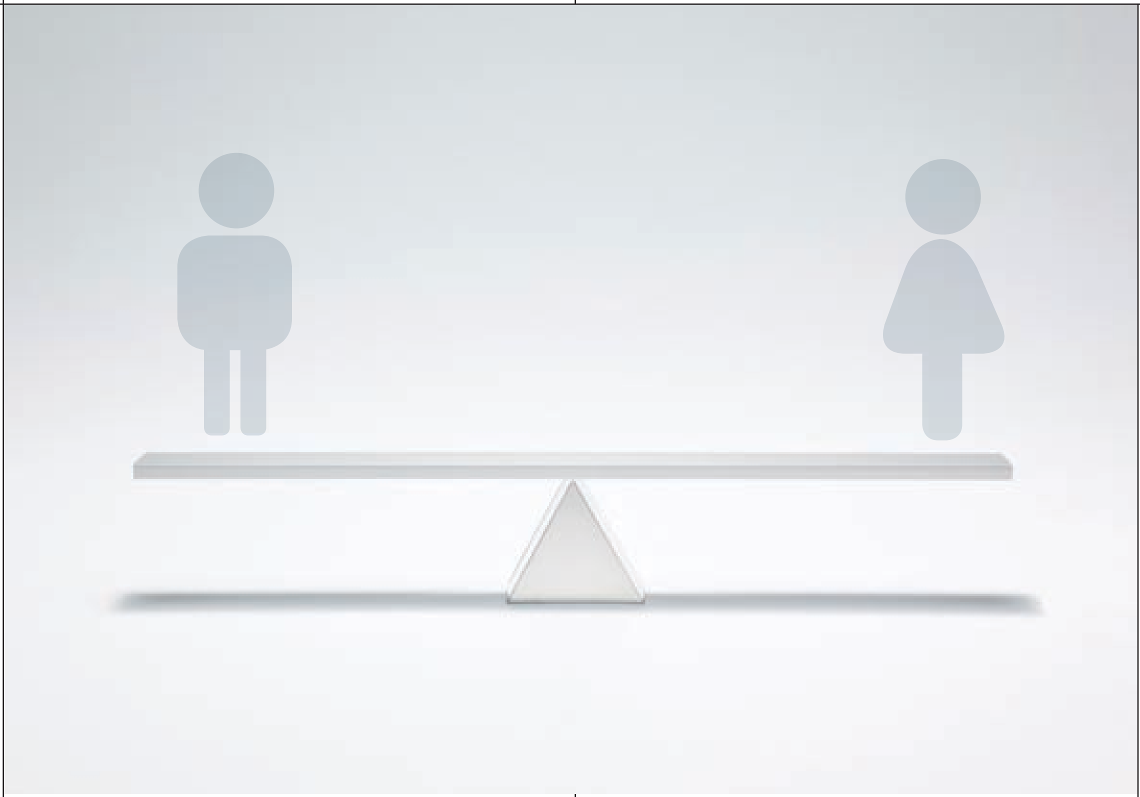
1» When passing on DNA to their offspring, mothers silence certain genes, and fathers silence others. These imprinted genes usually result in a balanced, healthy brain, but when the process goes awry, neurological disorders can result.

2» Imprinting errors are responsible for rare disorders such as Angelman and Prader-Willi syndromes, and some scientists are beginning to think imprinting might be implicated in more common illnesses such as autism and schizophrenia.

3» Even typical brains are the result of asymmetric contributions from Mom and Dad. Higher cognitive function seems to be disproportionately controlled by Mom's genes, whereas the drive to eat and mate is influenced by Dad's.

Stamps of Silence

The answer is genomic imprinting, as biologists discovered in the early 1990s. In a series of papers published in *Nature* and *Genes and Development*, researchers identified the first imprinted genes in mice, all related to a protein called insulinlike growth factor 2 (IGF-2), which plays a role in regulating the size of the pups. Mouse mothers silenced this gene, resulting in smaller, easier-to-carry fetal pups, whereas mouse fathers suppressed a gene that codes for the receptor for IGF-2's protein—blocking the receptor's suppressive action so that the pups could grow larger. Since that discovery, scientists have found more than 60 human genes that are



The imprinted genes we inherit from our parents exist in a delicate balance. If one parent silences more genes than the other does, the scale tips and complications arise—often affecting their child's brain and behavior.

PHOTOILLUSTRATION BY SCIENTIFIC AMERICAN MIND; GETTY IMAGES (*seesaw*)

typically imprinted by one parent or the other.

Genes are imprinted by the addition of molecules called methyl groups to the gene's DNA [*see box on next page*]. For reasons that are not totally understood, this methylation prevents the gene's information from being expressed, or transcribed into RNA and proteins, the basic building blocks of the body. It is as if the imprinting "stamp" blocks the gene's code from being read by the cell. A woman's egg carries only the genomic imprints that her mother passed on to her; her father's imprints are wiped away. Likewise, the genes that a man passes on in his sperm are imprinted in the same way that his father's genes were.

Normally, a mother's copy of a particular gene and a father's copy of the same gene are both expressed. When the genes differ (for instance, if Mom has blue eyes and Dad has brown), both genes are translated into proteins, and the end result is a combination of each gene's effects (the brown protein obscures the blue—although in reality several genes contribute to eye color). When a mother's gene is imprinted with a methyl group, however, it effectively becomes silenced—the mother's gene is then never expressed. Because only the father's gene product is being made, there is, in effect, half as much of that particular RNA or protein available to the body. Likewise, when a father's copy of a gene is imprinted, that gene is silenced, and only the mother's gene is used to make its RNA or protein.

Finding evidence of imprinting is tricky. If the two copies of a person's gene differ slightly in sequence, geneticists can analyze the RNA made from the gene to see if it, too, has two variants. If they find only one, then the gene may be imprinted, because one of the gene's copies was not expressed. If the researchers have access to the parents' DNA, they can verify which parent's gene was silenced. Because the discovery process is complex and time-consuming, scientists believe they have identified only a small fraction of the genes that are genomically imprinted. Nevertheless, many of the currently known imprinted genes influence the brain—explaining why, when imprinting goes wrong, it can cause profound effects on neurodevelopment.

Balance Skewed

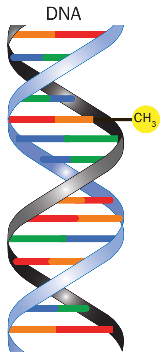
Among the rare disorders that result from imprinting errors is Angelman syndrome, which affects one out of 12,000 to 20,000 children in the world. Children with the syndrome are hyperactive and often smiling and laughing. In addition, studies suggest that more than 40 percent of affected kids suffer from autism spectrum disorders as well—experiencing great difficulty with language and social skills. The syndrome is marked by a reduction of maternally expressed proteins in a small section of chromosome 15, which is also usually paternally imprinted. In other words, genes from Dad are silenced as usual, but Mom's genes are also imprinted

How Genes Are Silenced

With genomic imprints, both parents' DNA is modified, controlling how it affects their offspring.

1

Egg



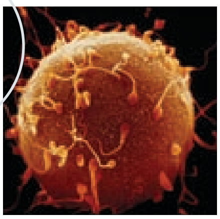
Mom's cells silence a gene by imprinting it with a methyl group (CH_3).

Sperm

Dad's cells silence a different gene.

2

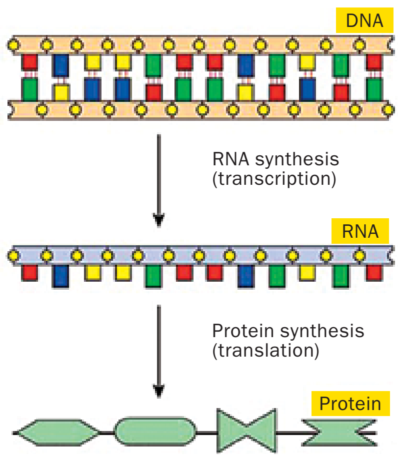
Zygote



Egg and sperm come together to form a zygote.

As the fetus develops, the genes that one parent silenced only get transcribed into RNA half as much as they would have with both parents' genes active.

During protein synthesis, a complex of previously fabricated proteins (*not shown*) reads a segment of DNA, using it to produce RNA, in a process known as transcription (*right*). Another set of molecules cooperates to translate the RNA into a protein (*lower right*).



3

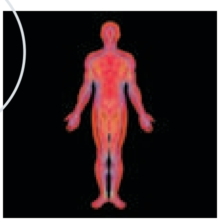
Fetus

Through development and even in adulthood, the pattern of activity in your genes depends on those initial imprints from each parent.

Most of these genes are expressed in the brain.

4

Adult



Finally, your body makes its gametes (eggs or sperm). The imprints on those cells' DNA revert back to what they were in your mother if you're female; your father if you're male.

Back to sequence 1!

Egg

Sperm

DAVID M. PHILLIPS *Photo Researchers, Inc.* (*egg and zygote*); SPL/PHOTO RESEARCHERS, INC. (*sperm*); M. A. ANSARY *SPL/Photo Researchers, Inc.* (*fetus*); CNRI/SPL/PHOTO RESEARCHERS, INC. (*infant brain*); SCOTT CAMAZINE *SPL/Photo Researchers, Inc.* (*adult*); EDMUND S. HIGGINS (*DNA helices and protein synthesis diagrams*) by mistake—they are not as active as they should be to balance Dad's imprinting effects. The brains of these children develop abnormally: their cerebral cortex is slightly smaller than usual, and a 2008 study in mice showed that cells in the cerebellum are also atypical.

When the imprinting balance is skewed in the other direction—too much net influence from Mom—another rare imprinting disorder results, called Prader-Willi syndrome, afflicting one in 10,000 to 25,000. It arises from a loss of paternal expression, caused by irregular imprinting, in the same region of chromosome 15 (although it can also result from a doubling of the mother's copy of chromosome 15). Magnetic resonance imaging studies of children with Prader-Willi syndrome reveal anomalies in the structure of their pituitary gland, a relatively small brain stem and atrophy in the cerebral cortex. Children with the disorder are mildly mentally retarded and exhibit hormonal problems, which often lead them to become obese as teenagers and adults.

Some scientists posit that imprinting problems are responsible for more than just rare developmental disorders. They could contribute to common mental illnesses that plague our society today, such as autism and schizophrenia. Sociologist Christopher Badcock of the London School of Economics, for instance, has a personal interest in autism that led him and his colleagues to investigate imprinting's effects on the disorder.

Opposite Disorders

Badcock has always thought that he sits a little closer to the autism side of the spectrum than most people do. "Modern diagnostic instruments suggest that quite a large proportion of the population is like this—particularly males," he explains. "The more I read about autism, the more I couldn't help noticing, I was probably one of those people, too." Over the years Badcock's interest in autism spawned a radical idea. "It suddenly struck me that there's this remarkable symmetry between the symptoms of autism and the symptoms of paranoid schizophrenia," he recalls. Autism, which translates from Latin roughly into "self-orientation," is characterized by impaired social interaction, gaze detection and language development. Psychotic disorders such as schizophrenia, on the other hand, can be considered the opposite: the lack of a sense of self in autism can be contrasted with megalomania often found in people with psychoses.

One day in 1993, while riding a commuter train in London, Badcock stumbled on an article in *New Scientist* about the role of imprinting in the expression of the gene for IGF-2, the protein that can affect a baby's size. Badcock suddenly realized that "insights into genomic imprinting could explain a lot about mental illness and whether you ended up autistic or psychotic," he says.

> When imprinting goes wrong, it **can cause profound effects** on neurodevelopment.

Badcock and evolutionary biologist Bernard Crespi of Simon Fraser University in British Columbia have since developed this theory, having most recently published an essay in *Nature* on the potential role that genomic imprinting plays in autism and psychotic disorders. "These disorders are opposites to one another, and imprinting is one of the mechanisms that can mediate that opposing feature," Crespi posits. Although imprinting usually builds a balanced brain, if one parent's contribution outweighs the other's, then autism spectrum disorders (the result of too much net paternal influence, they argue) or psychosis (the result of too much net maternal influence) may instead develop, they say.

Circumstantial evidence supports their theory. Autism is characterized by high birth weight, which one might expect if autism were caused by an overly paternally influenced brain, given the link between imprinting and growth-regulating genes. In addition, Angelman syndrome is marked by a larger net paternal influence, and 40 percent of Angelman sufferers also develop autism. Another rare disorder, Beckwith-Wiedemann syndrome, can be caused by several different alterations to a region along chromosome 11, one of which involves replacing the maternal copy of this region with an extra paternal copy. Children with this disease have a 10-fold increased risk of autism, according to a study published in 2008 by researchers at the University of St. Andrews in Scotland—suggesting yet again a link among imprinting, too much relative

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Battle of the Sexes

Genomic imprinting, in which certain genes are silenced by mothers and others by fathers, adds a layer of complexity to the traditional idea of inheritance. When imprinting goes awry, it causes terrible neurological problems—so why did it evolve in the first place? Evolutionary biologists have come up with several theories, but the one that is most widely accepted is the "parental conflict" idea. Developed by Harvard University biologist David Haig, this theory is based on two premises: first, that our ancestors, over time, evolved behaviors that helped them to pass on as many of their genes as possible to future generations. The second premise is that our female ancestors tended to have children with more than one man—and early male hominids impregnated as many females as possible.

If these assumptions are true, then according to the theory, it is in a male's evolutionary interest to create a baby that demands as much nourishment and attention as it can from its mother—at the expense of her other children, who were presumably sired by other men. Conversely, it is in a female's best interest to have children that are not overly demanding, because her goal is to distribute her resources equally among all her children so that they have the same chance of surviving.

These opposing forces, Haig says, battle each other through genomic imprinting. Mothers tend to silence genes that promote growth and demanding behavior, whereas fathers tend to silence genes that temper growth and demanding behavior. "There's this contrast in what they want from the pregnancy," says Anthony R. Isles, a behavioral geneticist at Cardiff University in Wales.

Some research on imprinting supports this theory: mothers often silence growth-related genes, which in effect halves the concentrations of the resulting growth-promoting proteins, and studies suggest that genes provided by fathers play a larger role in the development of brain regions involved in feeding and suckling than do genes provided by the mother. But although most researchers agree that this parental conflict theory explains the origins of imprinting, there is still only strong circumstantial evidence that it is correct.

—M.W.

AGE FOTOSTOCK

paternal influence and autism spectrum disorders.

Although there is no direct evidence that psychotic illnesses such as schizophrenia and bipolar disorder are the result of abnormal genomic imprinting in the other direction, there are nonetheless interesting hints of such a connection. For example, almost all children with Prader-Willi syndrome suffer from psychotic disorders.

Nondevelopmental diseases have been linked to imprinting in recent years, too. A study published in the *American Journal of Medical Genetics* in 2002 by Johns Hopkins University researchers reported that the gene variants that predispose people to late-onset Alzheimer's most often come from the mother, which could implicate imprinting. A study published in 1995 in the same journal found that bipolar disorder is also transmitted preferentially from the mother, and a study published in *Neurology* in 1997 found that Tourette's disorder has different symptoms and develops later if it is inherited from the father rather than from the mother—suggesting again (yet not proving) that imprinting may play a role in their development. "There are lots of dots that need to be connected still," says Jon Wilkins, an evolutionary theorist at the Santa Fe Institute.

If imprinting is solidly linked to the development of common mental disorders, then it may one day be appropriate to treat patients with drugs that manipulate gene expression. One method could be dialing down the activity of targeted genes, using a therapy called RNA interference—because it interferes with gene expression. A version of RNA interference that lowers the expression of growth-related tumor genes is currently being tested in a clinical trial in California and Texas. And two U.S. Food and Drug Administration–approved drugs for blood cell disorders, decitabine and azacitidine, prevent methyl groups from being added to genes in blood cells, demonstrating that this approach might help correct imprinting errors in other tissues as well. Although many effects of imprinting errors manifest themselves in the womb, treating imbalanced gene expression after birth could also reduce or eliminate some symptoms in these developmental diseases.

As scientists uncover imprinting's role in mental illness, they are also revealing some intriguing asymmetries in each of our parents' contributions to our brain and behavior. In two landmark studies published in 1995 in the *Proceedings of the National Academy of Sciences USA* and in 1996 in *Developmental Brain Research,* Cambridge developmental biologist E. Barry Keverne and his colleagues discovered that certain brain regions are almost entirely controlled by the mother's genes and other regions by the father's. After the researchers created normal mouse embryos consisting of only a few cells, they combined them in a petri dish with two-celled embryos comprising either solely paternal or solely maternal chromosomes. The resulting fetuses consisted of either mostly paternally or mostly maternally expressed genes.

The mice with more paternal influence had smaller brains and larger bodies, and brain cells grew abundantly in the hypothalamus and septum—areas that maintain energy balance and mediate behaviors such as food seeking, mating, emotional expression and social aggression. Conversely, mice bred with more maternal influence had smaller bodies and larger brains—especially forebrains and regions that are involved in intelligence, complex emotional responses, planning and problem solving.

Like Father, Like Son

These findings suggest that Dad's genes play a bigger role in the development of instinctual behaviors, such as feeding and mating, whereas Mom's genes are more concentrated on the development of higher-order cognition. "The maternal influence is more on language and social executive function aspects of the brain, which are, in a sense, more complex," LaSalle explains.

Psychological research in humans also bolsters these data. In a 2006 study published in the *Journal of Neurogenetics,* psychologists at Baycrest Hospital in Toronto recruited families composed of an adult brother and sister and their biological parents. The researchers gave them tests made up of tasks that depended on particular brain regions. The siblings performed much like their mothers did on tasks that involved the frontal and parietal lobes and the hippocampus, suggesting that skills using those areas come from the mothers. The authors admit, however, that kids might also resemble their mothers in these types of skills because of how much time they spend with their moms during childhood.

What is irrefutable, however, is that genomic imprinting has overturned some of the most basic tenets of biology. A century's worth of research in genetics, developmental biology and neuroscience was based on inheritance concepts that are simply not true—which means that we know far less about the brain than we thought we did. "We've got a bunch of new stuff that, fundamentally, we don't even know how to get our minds around," Wilkins admits. We can no longer think of ourselves as rough composites of our parents but rather as intricate puzzles crafted from thousands of maternal and paternal pieces over the course of evolution. And once we identify all the parts—which will be a huge challenge in itself—we will then need to decipher how they fit together. "It's just going to take time," Wilkins says. **M**

(Certain brain regions are **almost entirely controlled** by the mother's genes, and other regions by the father's.)

Mice with more paternal genes have brains with healthy food- and sex-related areas but abnormally small regions involved in problem solving, intelligence and planning. Maternally influenced mice are the opposite.

(Further Reading)

- **Imprinted Gene Expression in the Brain.** William Davies, Anthony R. Isles and Lawrence S. Wilkinson in *Neuroscience and Biobehavioral Reviews,* Vol. 29, No. 3, pages 421–430; May 2005.
- **Imprinted and More Equal.** Randy L. Jirtle and Jennifer R. Weidman in *American Scientist,* Vol. 95, No. 2, pages 143–149; March–April 2007.
- **Battle of the Sexes May Set the Brain.** Christopher Badcock and Bernard Crespi in *Nature,* Vol. 454, pages 1054–1055; August 2008.
- **Genomic Imprinting and Human Psychology: Cognition, Behavior and Pathology.** Lisa M. Goos and Gillian Ragsdale in *Advances in Experimental Medicine and Biology,* Vol. 626, pages 71–88; 2008.