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Tug of War Pits Genes of Parents in the Fetus

By NICHOLAS WADE

Under Mendel's laws of inheritance, you could thank mom and dad equally for all the outstanding qualities you inherited.

But there's long been some fine print suggesting that a mother's and father's genes do not play exactly equal roles. Research published last month now suggests the asymmetry could be far more substantial than supposed. The asymmetry, based on a genetic mechanism called imprinting, could account for some of the differences between male and female brains and for differences in a mother's and father's contributions to social behavior.

A person gets one set of genes from each parent. Apart from the sex chromosomes, the two sets are equivalent, and in principle it should not matter if a gene comes from mother or father. The first sign that this is not always true came from experiments in which mouse embryos were engineered to carry two male genomes, or two female genomes. The double male and double female mice all died in the womb. Nature evidently requires one genome from each parent.

Biologists then made the embryos viable by mixing in some normal cells. The surprising outcome was that mice with two male genomes had large bodies and small brains. With the double female genome mice, it was the other way around. Evidently the maternal and paternal genomes have opposite effects on the size of the brain.

The root of the asymmetry is a procedure called imprinting in which either the mother's or the father's copy of a particular gene is inactivated. The best worked out example concerns a gene called insulinlike growth factor-2, which promotes the growth of the fetus. The IGF-2 gene is active in the paternal genome but imprinted or inactivated in the genome the fetus receives from its mother.

The leading explanation for imprinting is a theory that invokes conflict between relatives.

Developed by David Haig, an evolutionary biologist at Harvard, the theory holds that there is a clash of interests between the fetus, whose purpose is to extract as much nutrition as possible, and the mother, whose interests lie in allocating her resources evenly to all the other children she may bear in the future.

Over the course of evolution this conflict has come to be mediated at a genetic level, Dr. Haig's explanation goes, because the mother and the father have different interests. Speaking of mammals in general, the conflict is driven by female promiscuity. The mother wants to share her resources among progeny who may have different fathers, whereas the father is interested in the survival of only his own child. So the father always confers the IGF-2 gene in active form and the mother always bequeaths it in imprinted or silent form. The gene is imprinted in mice, humans and many other mammals.

It may seem strange to have a genetic tug of war within the fetus, with the paternal copy of the IGF-2 gene always asking for more, and the maternal copy refusing to ask at all, but presumably over the course of evolution the individuals who carried these two warring copies of the gene left more offspring than those with the gene in any other form.

Until last month only a hundred imprinted genes were known, and the mechanism seemed just an interesting deviation from Mendelian genetics. Research led by Christopher Gregg and Catherine Dulac of Harvard has shown that imprinting is far more common and more intricate than supposed.

Working in mice, the Harvard team showed that around 1,300 genes are imprinted. Dr. Dulac said that she expects a substantial, though lesser, proportion to be imprinted in people — maybe some 1 percent of the genome — because humans are more monogamous than mice and so the parents' interests are more closely aligned.

Dr. Dulac was able to detect so many new imprinted genes by taking advantage of the ease with which genes can now be decoded. She cross-bred two very different strains of mice, thus ensuring that the maternal and paternal versions of each gene would have recognizably different sequences of DNA.

When a gene is activated, the cell transcribes it into RNA, DNA's close chemical cousin. By decoding all the RNA transcripts in the mouse's cells, Dr. Dulac could pick out those genes in which the paternal version was being transcribed much more than maternal version, and vice versa.

Besides finding far more imprinted genes than expected, Dr. Dulac's team also picked up

unexpected patterns in the way the genes were expressed. Maternal genes were more active in the embryo's brain, but paternal genes became more active in the adult.

In another novel pattern, she found sex differences in imprinted genes in different region of the brain, particularly those concerned with feeding and with mating behavior. A gene called interleukin-18 is activated from the mother's version in two important regions of the brain. This asymmetry is of interest because the gene in people has been linked with multiple sclerosis, a disease that predominates in women.

Altogether Dr. Dulac found 347 genes where either the mother's or the father's copy was more actively expressed in certain regions of the brain. Sex differences in the brain are usually attributed to the influence of hormones, but sex-based differences in imprinting may be another mechanism by which nature spins male and female brains out of the same genome.

"In your brain, your mom and your dad keep telling you what to do — I keep laughing when I think about it," Dr. Dulac said.

In the cortex of the brain, Dr. Dulac discovered another unexpected asymmetry. Women have two X chromosomes, one from the mother and one from the father. The usual rule is that in each cell either the mother's or the father's copy is chosen at random to be switched off. But in the neurons of the cortex, there is a much greater chance that the paternal X chromosome will be switched off. "So again, it's the conflict between mom and dad — each tries to use different chromosomes to influence you," Dr. Dulac said.

Dr. Haig says that his theory of imprinting explains not only the tug of war between mother and fetus but also why there are imprinted genes in the brain.

It all has to do with the different interests of the mother's family and the father's family, which tug the individual in different directions. Relatives get into the argument because they share varying proportions of an individual's genes.

Evolutionary fitness depends on passing one's genes on to the next generation. But it also counts to pass on the identical genes that have been co-inherited by one's siblings, uncles and aunts. The doctrine, known as inclusive fitness, was proposed by the biologist William Hamilton in the 1960s and is widely accepted, though is not without critics. It was challenged last month in the journal Nature by the Harvard biologist E. O. Wilson and two colleagues.

Under inclusive fitness, Dr. Haig has pointed out, a conflict of interest between the mother's and father's relatives would have arisen because of the different dispersal patterns of men and women. Most often it has been the woman who leaves her ancestral village and goes to live with her husband's family.

The maternal genes stand to gain if the woman is as selfish as possible and focuses just on her and her children's welfare. But since the father is related to everyone else in the village, the father's genes will gain from altruistic behavior. Such a conflict will result in imprinted genes, just like the battle between the mother and fetus over the mother's resources, in Dr. Haig's view.

Two evolutionary biologists, Francisco Ubeda of the University of Tennessee and Andy Gardner of the University of Oxford in England, have devised a mathematical model for assessing the consequences of a woman living in her husband's village, among people to whom she is not related. Natural selection, they say in an article in the current issue of Evolution, will favor the activation of paternal genes that underlie altruistic behavior and maternal genes that promote selfishness. "Your paternal genes want you to be nicer to your neighbors than your maternal genes do," Dr. Gardner said in an interview.

In most people the altruistic and selfish motives operate in some reasonable kind of balance. But the imprinted genes carry a serious vulnerability: since they are silenced, a mutation to the other copy can be disastrous. Diseases like autism may be connected with disruptions to imprinted genes, Dr. Gardner said.

Imprinting, far from being a genetic curiosity, may play a central role in sexual differences and in psychiatric disease, if Dr. Haig's explanation is correct. Much of the available evidence comes from mice, and people may to some extent have emancipated themselves from imprinting when they evolved the pair bond system of mating about a million years ago. But the pair bond does not mean perfect monogamy, and in its deviations from perfection there is plenty of room for imprinting to thrive.