Chip off the old block? Fathers pass along more of their DNA, disease problems and all

Everybody is familiar with the story of how King Henry VIII blamed his wives for miscarriages and for the illnesses of his babies that actually survived. Even more famous is the story of Henry wanting sons, but his wives gave birth only to daughters. He could not influence the babies' gender; that much is certain, since gender depends on whether the father contributes an X or a Y chromosome. But what about the illnesses? Possibly, Henry could have been the reason for those too.

Over the last few years, geneticists have come to think that the father's genes may be more powerful than the mother's genes in affecting the child's health. Studies show that fathers often may be the reason why certain mothers lose their pregnancies. In some cases, fetal blood proteins made from genes that the fetus received from the father become targets of the mother's antibodies. In a sense, the mother's immune system attacks the fetus in her womb, because of the paternal component of the fetal genome. The mother then experiences a spontaneous abortion ("miscarriage"). Since several of Henry's wives miscarried, it's more reasonable to think that Henry's genes were to blame, rather than to think that all of his wives had a similar problem.

As for illness in babies that do make it through a pregnancy, until recently, paternal genes have appeared to be more 'powerful' than maternal genes when it comes to health; men are more likely to pass along certain, specific genetic illnesses.

Of course, mothers and fathers provide equal amounts of nuclear DNA –genes in the cell nucleus– to their children, which leaves each individual with an interesting mix. But a new study, published in the prestigious journal *Nature Genetics*, says that we actually *use* more of the paternal DNA than the maternal.

"This is an exceptional new research finding that opens the door to an entirely new area of exploration in human genetics," according to the senior author of the study, Fernando Pardo-Manuel de Villena, of the University of North Carolina School of Medicine.

New appreciation of an old concept

Geneticists have known that gene-gene interactions impact dramatically which genes are expressed and how powerfully. Receive a mutation for a certain disease from one parent and the gene behaves one way; receive the same gene from the other parent and it behaves differently. That difference can determine whether you get sick or your level of disease risk, and for years genome research has been uncovering disproportionate paternal genetic contributions to various diseases. Back in 2000, for example, a big study conducted in London and published in the journal *Diabetes* found that a certain dysfunctional gene has a more powerful effect in causing Type-2 diabetes, if it comes from the father rather than from the mother. During the last decade, the role of paternal genes also has been a major research topic in connection with heart disease in major journals, such as the *Journal of the American Medical Association* (JAMA). Overthe years, diseases influenced more by paternal than maternal genes have been uncovered, gene-by-gene, disease-by-disease.

Up until now, however, the phenomenon was thought to apply to fewer than 100 genes. The new UNC study is different, because it shows that the number of genes that work this way actually is in the thousands. In other words, the action of a major fraction of your genes really does depend on who gave them to you. This matters particularly when it comes to genes that vary a lot –exist as different mutations. That's because a big focus of medicine today is on which mutations cause which diseases. It turns out that the genes with a higher variety of mutations tend to be expressed more completely when they're inherited from father rather than from mother.

While the UNC study was conducted on mice, and not humans, the team believes the results speak volumes in terms of the interplay between maternal and paternal genes for all mammals, including our own species.

"Imagine that a certain kind of mutation is bad," says Pardo-Manuel de Villena. "If inherited from the mother, the gene wouldn't be expressed as much as it would be if it were inherited from the father. So, the same bad mutation would have different consequences, depending on whether it has been inherited from the mother or from the father."

Too early to jump to conclusions

Before society begins worrying too much about the paternal contribution of disease genes as compared with the maternal contributions, let's keep in mind –as always– that genetics is complicated. The more we uncover new genetic mechanisms, the more we learn that the devil is in the details. In the case of heart disease, for example, the evidence is conflicting. While paternal genetics has been the focus of research, a big study published in the journal *Heart* in 2003 suggested the opposite –that the mother's genes could be *more important* than the father's when it comes to one's risk for coronary artery disease.

Coronary artery disease is not the only case for which the maternal hereditary issue is paramount. Moreover, things get still more complicated when we consider the growing understanding of paternal genes in relation to disease genes that affect only, or mostly, females. Let's look at the BRCA genes (*BRCA1* and *BRCA2*) for breast cancer and ovarian cancer. Particularly prevalent in Ashkenazi Jews, Norwegians, Dutch, and Icelanders, having these genes in one's family increases one's risk of developing

several cancers, especially of the breast and ovary. *BRCA* 1 and 2 can increase the risk of male breast cancer (rare but it occurs), but otherwise the health issue is really cancer in women. How the new UNC discovery on paternal genes will affect how we view female genetic diseases is highlighted by this case made by GLP's Jon Entine in the first chapter of his book on the shared ancestry of Jews, Christians, and Muslims, *Abraham's Children*.

> My mother, aunt, and grandmother died of ovarian or breast cancer. Both of my sisters are breast cancer survivors and we all carry the BRCA2 mutation. But the impact of inheriting that falls a lot harder on my sisters than me…except that I have a daughter and she inherited it as well do suggest that *we have gaping holes in our* our understanding of genetics and disease continues to grow.

While there certainly still are gaping holes in our genetic knowledge, in terms of disease genes, the trend in discovery says that the father's role is significant. So at least we can conclude that Henry VIII had no grounds to blame the illnesses of the children on their mothers.

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