Biological Psychiatry: Celebrating 50 Years

Leaping Forward: The Surprising Role of Jumping Genes in Psychiatric Genetics

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What can your DNA say about your health?
–Internet advertisement for personal genetic testing

Just three simple steps: place your order online, spit into a tube, and 3 to 5 weeks later, log in to "start discovering what your DNA says about you." Along with information about your ancestry, you get personalized reports about how your DNA has shaped who you are—from your ability to match musical pitch to whether you have a unibrow. More impressively (so you are told), your DNA tells you about your risk of cancer, diabetes, and even Alzheimer's disease. It is seemingly a marvel of modern technology—the embodiment of how far and how fast the world is changing.

The first human genome was sequenced in 2001. It took 13 years and cost $2.7 billion. Today, genomes can be sequenced routinely, in a day or two, for less than $1000 (1). Genetic testing has become so cheap and accessible that it has spawned an entire industry of direct-to-consumer products. The premise is simple: extract DNA from cheek cells in saliva and test it for common, inherited variations that cause (or heavily influence) a given trait or disease. Voilà!

The tests are predicated on the basic understanding of genetics that began more than 100 years ago with Gregor Mendel. In studying pea plants, Mendel discovered that certain traits, such as height and flower color, were coded for and passed on from one generation to the next in what we now know as genes. Each person has a unique genetic code, made up of about 20,000 protein-coding genes, formed when an egg and sperm meet to create a single cell. That same code is replicated countless times through development. It serves as the instruction manual by which proteins are made. These proteins perform all functions in the body.

Once this was worked out, it was natural for researchers to attempt to understand diseases by looking for mutations that might disrupt the production or function of specific proteins. Initially, researchers looked for single mutations in single genes—with early successes for medical diseases like cystic fibrosis. But these approaches gained little traction in psychiatry. Though psychiatric illnesses are known to have high heritability, few follow simple Mendelian principles. More illnesses are thought to follow complex patterns of inheritance, with many genes acting together, each contributing a very small amount. (This is the primary reason why direct-to-consumer tests are of grossly limited utility.) The environment is also known to play an important role, including through epigenetic mechanisms, wherein the environment shapes the expression of genes (2).

There is a key assumption underlying all these models: that every cell in the body is using the same genetic template to create the proteins that perform essential bodily functions. Only recently has research illustrated that there may be an entirely different process going on.

Of all places, the story began with an ear of corn (3,4). In the 1940s, Barbara McClintock was studying plant genetics. Corn is an especially interesting model species: each ear contains several hundred egg cells; after fertilization, each of these cells divides many times to develop into an individual kernel—which is to say that a full ear of corn is actually a collection of embryos (kernels), each of which descended from a single fertilized egg.

In many ways, McClintock's work was directly following Mendel's. While studying kernel color, she identified a dominant allele that could inhibit color from being expressed—any kernel with that allele would be clear. McClintock was perplexed when she ran an experiment with genetically identical kernels, all expressing the inhibitor, and found that some were developing with different colors. Quite simply, this should not have been possible.

Based on classic Mendelian genetics, McClintock understood genes to be a series of stable entities arranged on chromosomes like beads on a string. But when she looked deeper, she discovered something astonishing: a certain part of the chromosome was able to move; when moving, this element could insert itself within other genes and thereby disrupt their functioning. What this meant was that even though all the cells in an individual kernel were descendants of the same single fertilized egg, they could still turn out to be genetically different. They were not mutating as in cancer—they were actually shuffling pieces of DNA back and forth. Moreover, if the piece that moved (the mobile element) landed within the inhibitor allele, it could prevent it from functioning. This is how kernels that were supposed to be clear were colored.

And not only could this element move, it could move at any time during the kernel's development and at any stage in cell division. If the movement happened early in development, a high proportion of cells within the kernel could turn out to be colored. If it never moved at all, the dominant inhibitor allele would function as expected and the kernel would be entirely colorless.

This idea—that genes could literally get up and move to another part of the genome—was so bizarre that it was ignored. It challenged the longstanding dogma that an organism's genes are stably arranged, faithfully duplicated from one cell division to the next. Other scientists at the time thought that there was no way this could be real. The idea that

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DNA could move seemed as ridiculous to McClintock's contemporaries as had Galileo's declaration, 400 years earlier, that the Earth moved.

But it did. And the extent of transposable elements (TEs), informally known as "jumping genes," was far more widespread than McClintock or anyone else could have imagined. It was not until the 1960s and 1970s that other researchers discovered TEs in simple species like bacteria, yeast, and bacteriophages. In fact, it turns out that these elements are present in virtually every eukaryotic genome sequenced to date (3,5).

TEs are classified into families depending on how they move through the genome (Figure 1) (5). Like the elements discovered in corn, one particular family called long interspersed nuclear elements (L1) can move at any time during cell division, including in egg and sperm cells before fertilization. And, of all places, L1s have been shown to be more abundant in brain cells than in other cells in the body. Not only are they active during brain development, but mounting evidence suggests that they can also mobilize in nondividing neurons. While we have always thought brain cells to be genetically identical, this process can lead to populations of genetically different cells (6,7). Much like the splotchy kernels in the corn, any L1-induced DNA variant in a neuronal precursor will only be present in its daughter cells.

There appears to be a baseline amount of jumping that happens naturally and without consequence during development. It is hypothesized that this cellular diversity may contribute to differences in behavior and cognitive functioning between people (7,8). But this jumping is generally well contained (through a combination of transcription factors and chromatin modifiers); if the process occurred too frequently, it would interfere with any number of genes and processes that are crucial to survival (7,9).

But there are times when the ordinary regulatory balance may shift. In her work in corn, McClintock noticed that the elements were more likely to move when the corn was stressed. Perhaps this reflected an adaptive response: a way in which the organism could respond to an environmental challenge. Today, more research has corroborated the idea that environmental factors, such as drug use and stress, can influence levels of transposition in the brain (6).

While this research is still in its infancy, it is clear that TEs may play a critical role in certain psychiatric illnesses (6,7). If a TE inserts into a gene critical for a particular function, this

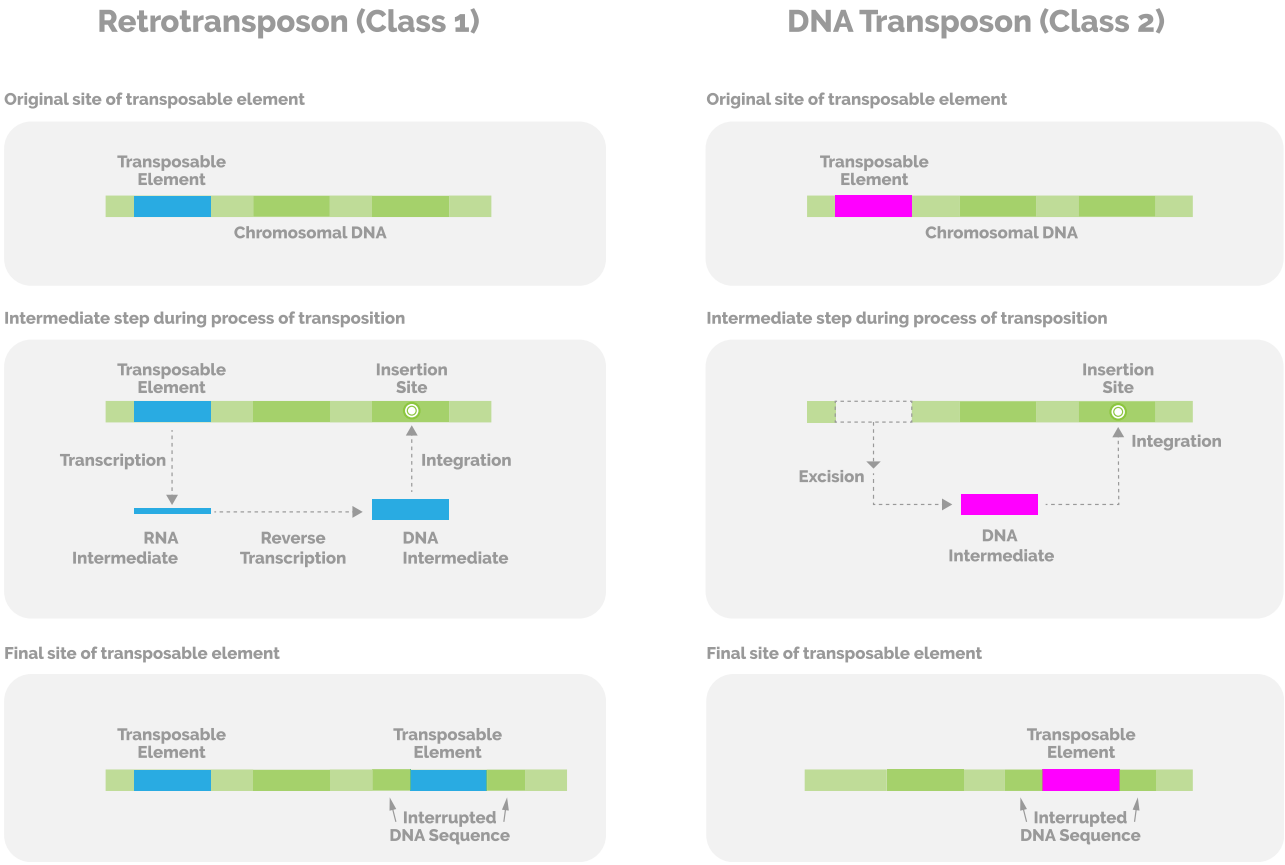

Figure 1. Transposable elements are divided by mechanism into two classes. Class I, also called retrotransposons, is the class to which long interspersed nuclear elements belong. These elements share characteristics with retroviruses and move through a "copy and paste" mechanism: first an RNA intermediate is formed; this intermediate is then converted back into a DNA copy that can insert into another location in the genome. Class II transposable elements are known as transposons; they do not use an RNA intermediate and typically transpose via a cut and paste mechanism where the DNA element is first excised and then moves (though some do exist that make a DNA copy first).

could contribute to disease pathophysiology. For example, patients with schizophrenia have been found to have a higher number of retrotransposon insertions in the prefrontal cortex compared with healthy control subjects. Examining the specific genes in which the L1s were inserted revealed genes involved in synaptic function as well as genes already implicated in schizophrenia.

TEs may also play a significant role in substance use disorders (6). Postmortem brains from cocaine-addicted individuals showed L1 insertions in genes known to be relevant to cocaine addiction that were not present in non–cocaine-addicted control subjects. In this case, it may be difficult to know whether the TEs were the cause or the effect of the addictive disorder—or, as is often the case, perhaps both are true.

So what can your DNA say about your health? A lot. Modern genetics is offering unprecedented insights into the intricate ways that our genes and environment shape who we are (10). But what can direct-to-consumer products tell you about your health? For now, especially in psychiatry, they seem to be more symbol than science—and one reason (among many) is the surprising realization that the DNA in your cheek may actually be different from the DNA in your brain.

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