It's not ALL in the Genes: The Epigenetics of Neuropsychiatric Disorders

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You've probably heard the term "epigenetics" somewhere, but what is epigenetics anyway? Epigenetics is basically the study of changes in gene expression that are NOT caused by changes in the DNA sequence. Epigenetic changes influence how your body reads a gene sequence and can determine whether each gene will be expressed or not. Biologists have even found that we can inherit traits from our parents resulting from epigenetic changes acquired in their lifetimes.

Before we dive deeper into epigenetics and how they relate to neuropsychiatric disorders, we need to cover some background on DNA and gene expression. DNA is a linear code made up of individual molecules called nucleotides. Series of nucleotides within our DNA code form each gene. In each of our cells, we have about 3 billion nucleotides worth of DNA—contained within that DNA are nucleotides that code for about 20,000 individual genes. Most genes in our DNA code for products (usually proteins) that perform specific functions throughout the cell. Thus, when someone refers to the "function of a gene," they are usually referring to the function of the protein encoded by that gene.

If you were to measure the length of DNA within each of our cells, you might be surprised to find that its three billion nucleotides extend two meters (six feet) in length! To fit inside cells that are measured in nanometers, the DNA is wound around protein spools (called histone proteins), similar to cassette tapes. This clever packaging not only allows DNA to fit into each our tiny cells, it turns out the histone proteins that the DNA is wound around can also influence gene expression.

Epigenetic changes affect gene expression by acting as tiny light switches, which act as on/off switches for gene expression. There are different types of epigenetic marks—

which are all small chemical modifications—that affect gene expression. Epigenetic marks often direct the histones to wind or unwind a certain region of the DNA, which ultimately influences what genes will be expressed. When DNA is unwound from the histone, the genes in the unwound regions are expressed. If the DNA remains wound around the histone spools, it cannot be accessed by the cellular machinery that causes gene expression, thereby causing genes in those regions to be repressed or inactivated.

All of the cells in our body have essentially the same DNA code. What distinguishes one organ from another are the types of genes that are turned on or off, a process which is largely controlled by epigenetic marks. Thus, epigenetic regulation has been connected to critical functions throughout our body, including brain development and brain function. Dysregulation of epigenetics has been connected to a number of devastating conditions, including neuropsychiatric disorders [1].

Neuropsychiatric disorders, such as bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia, are complex disorders that involve both neurology and psychiatry and include a broad range of symptoms. Although neuropsychiatric disorders can greatly differ from one another, they often share overlapping causes [2]. For example, emerging evidence indicates epigenetics is involved in their pathophysiology; in other words, dysregulated epigenetics contributes to the abnormal brain development and disrupted brain function associated with neuropsychiatric disorders. One interesting study that highlighted the role of epigenetics in neuropsychiatric disorders involved identical twins [4]. Although the twins had almost identical genetic material, only one twin suffered from schizophrenia. The affected twin displayed a dysregulation in certain epigenetic marks involved in pathways linked to psychiatric disorders and brain development [3].

There are currently no cures for neuropsychiatric disorders. Current therapies—which often include a combination of medication and behavioral therapy—can improve the

symptoms of neuropsychiatric disorders, but the effects are not permanent. One example is the class of drugs known as mood stabilizers. The neurotransmitter serotonin is involved in regulating mood and behavior and can be heavily dysregulated in neuropsychiatric disorders. Mood stabilizers function by temporarily increasing serotonergic signaling in the brain—for example, by increasing serotonin receptors. Unfortunately, this effect is temporary, and the medications are only effective in some individuals.

What if instead of using medications there was a way to manipulate neurologically relevant epigenetic marks for artificial induction (or repression) of gene expression? For example, what if there was a way to use epigenetics to permanently increase the level of serotonin receptors? This is not science fiction, there is a way.

CRISPR/Cas9 is a powerful genetic tool that could be used to alter epigenetic expression of genes in individuals suffering from these debilitating disorders. Think of it as a genetic-engineering guided missile. The CRISPR part is the homing device that guides molecular scissors (the Cas9 enzyme) to a target section of DNA. Together, they work to disable, repair, or activate a target gene. This system can be modified by using a deactivated Cas9 (dCas9), one that only targets and binds, but will not cut, DNA. It can be used to introduce controllers, that can direct the removal or addition of epigenetic marks, to cause or prevent gene expression.

Studies have shown that changing epigenetic marks of genes within neurons located in the reward center of the mouse brain can control behavioral responses evoked by drugs and stress [5]. These changes could even influence addiction and depression-related behaviors [5].

Manipulation of epigenetic marks shows great therapeutic potential for neuropsychiatric disorders, and even holds the promise of a lasting cure. While more

research must be conducted to ensure this approach is safe, news of a potential cure provides hope to those suffering from these illnesses and for the people who love them.

References

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