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Undergraduate

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# FROM ONE LIFE TO ANOTHER - THE STRESS THAT DEFIES TIME

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BY LEANDRA PADAYACHEE

With accumulating academic, financial, and personal responsibilities, no college student is a stranger to the idea of stress - that feeling of overwhelming anxiety constantly nagging the mind. However, could there be a chance that this “stress” was passed down from our parents, or even grandparents? The idea of gene modification from environmental influences has been studied numerous times, yet the proposal of this alteration being passed down to succeeding generations is a novel concept entirely. Recent research with mice and human subjects reveals that when negatively influenced by a certain external trauma, both species could genetically transfer these sensitivities to their offspring. Yet how can a parent’s “fear” be biologically passed down?

According to conventionally accepted scientific information, the genetic sequences contained in DNA are the only way to transmit biological information across generations. Random DNA mutations, when beneficial, enable organisms to adapt to changing conditions, but this process typically occurs slowly over many generations.<sup>1</sup> However, the theory of epigenetics, or the study of heritable changes in gene expression, does not involve changes to the underlying DNA sequence. Epigenetic change occurs from the addition of methyl (CH<sub>3</sub>) groups to certain locations on the DNA molecule, which in turn silences parts of the gene in a particular pattern and leads to a specific modification of the gene’s phenotype. The

DNA code itself is not changing; it is the parts of the expressed DNA code that undergo alteration. This process is called DNA methylation, and can ultimately be influenced by several factors including age, disease, and the environment.<sup>4</sup>

Although the epigenetic concept of DNA methylation has been scientifically proven, the idea of transmitting these alterations from generation to generation is still debatable, especially in such complex subjects as humans. One controlled experiment with mice, however, found that when a mouse learns to become afraid of a certain odor, its pups will be more sensitive to that odor, even though the pups will have never encountered it themselves.<sup>3</sup> Researchers Kerry Ressler and Brian Dias studied epigenetic inheritance by training laboratory mice to fear the scent of acetophenone through the pairing of odor exposure with electric shocks. This Pavlovian fear conditioning ultimately increased sensitivity in the mice’s olfactory bulb; however, the researchers also discovered that the naïve adult offspring of the sensitized mice inherited the same behavioral sensitivity to the smell.<sup>2</sup> According to Dias, “[t]he inheritance takes place even if the mice are conceived by in vitro fertilization, and the sensitivity even appears in the second generation (grandchildren). This indicates that somehow, information about the experience connected with the odor is being transmitted via the sperm or eggs.”<sup>3</sup> The researchers proposed that DNA methylation explains the inherited sensitiv-



ity - the acetophenone-sensing gene of sperm cells had fewer methylation marks, which could have led to greater expression of the odor-receptor gene for the mice offspring. However, the research poses some unanswered questions in the end. For example, the reversibility of the effect is unknown – if sensitized parents later learn not to fear an odor, the effects on their pups still remains unknown. Another limiting factor is that the epigenetic research only involved the smell receptors. What about the other senses – sound, taste, etc?<sup>3</sup> This research is relatively new, so we can only wait and see how Dias and Ressler continue their trans-generational research.

Testing generational epigenetic inheritance with laboratory mice seems to be the best method for proving the theory of epigenetics, due to the experiment's extremely controlled environment. Moreover, attempting this research on human patients remains very controversial, since controlled studies are neither feasible nor ethical – people are constantly influenced by social interaction as well as biological inheritance, so separating the two would prove more than difficult. Nonetheless, in a recent 2015 experiment, researcher Rachel Yehuda studied survivors of

the Holocaust as well as their offspring to test the transmission of stress from epigenetic mechanisms. Yehuda conducted research both on Holocaust victims struggling with post-traumatic stress disorder (PTSD) and on their unaffected children, and ultimately found that the traumatic exposure to the Holocaust had an effect on FK506-binding protein 5 (FKBP5) methylation in both generations, a correlation not found in the control group and their children.<sup>5</sup> FKBP5 is an immunophilin protein, which means it plays a role in regulating the immune system. This gene is known to code for major depressive disorder since it interacts with the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is a complex biological mechanism that controls the body's reaction to stress, and is strongly linked to the neurophysiology of depression.<sup>7</sup> According to Yehuda, the FKBP5 methylation in Holocaust parents was found specifically on bin 3/site 6, specific sites on the gene associated with psychological childhood stress – an alteration most likely due to the trauma from the Holocaust. Contrasted with the parents, however, the offspring showed methylation on bin 2/sites 3 to 5, a location on the gene receptor typically associated with childhood physical and sexual abuse.<sup>6</sup> Despite these subjects having no history of such abuse, the FKBP5 methylation nevertheless occurred, prompting Yehuda to attribute these outcomes to transgenerational epigenetic inheritance. The researcher ultimately reported in her experimental conclusion that “the findings suggest the possibility of site specificity to environmental influences, as sites in bins 3 and 2 were differently associated with parental trauma and the offspring's own childhood trauma, respectively.”<sup>6</sup> Although her research encompasses only a limited number of subjects and can be criticized ethically, Yehuda has presented



Image of laboratory mouse with her offspring. Researchers Kerry Ressler and Brian Dias studied epigenetic inheritance by training laboratory mice and observing biological effects on the subsequent pups.



Image of children during the Holocaust. Researcher Rachel Yehuda studied both survivors of the Holocaust and their offspring to test the transmission of stress from epigenetic mechanisms.



the scientific community with the radical idea of trans-generational stress inheritance not just in animals, but in people as well.

In the end, these mice and human research experiments truly offer the scientific community crucial data for future experimentation. Even Ressler claims that “[k]nowing how the experiences of parents influence their descendants helps us to understand psychiatric disorders that may have a trans-generational basis, and possibly to design therapeutic strategies.”<sup>3</sup> But although these experiments suggest DNA methylation as the source behind generational stress inheritance, more research must be done to fully understand the molecular mechanism of such results. With further studies, we may finally be able to differentiate the border between environmental influence and biological influence, and potentially develop preventative treatment for psychiatric patients in the future.

“Knowing how the experiences of parents influence their descendants helps us to understand psychiatric disorders that may have a trans-generational basis”

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