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Trauma's epigenetic fingerprint observed in children of Holocaust survivors

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The children of traumatized people have long been known to be at increased risk for posttraumatic stress disorder (PTSD), and mood and anxiety disorders. However, according to Rachel Yehuda from the James J. Peters Veterans Affairs Medical Center at the Icahn School of Medicine at Mount Sinai who led a new study in *Biological Psychiatry*, there are very few opportunities to examine biologic alterations in the context of a watershed trauma in exposed people and their adult children born after the event.

One of the most intensively studied groups in this regard are the children of survivors of the Nazi concentration camps. From the work of Yehuda and others, there has been growing evidence that concentration camp survivors and their children might show changes in the epigenetic regulation of genes.

Epigenetic processes alter the expression of a gene without producing changes in the DNA sequence. DNA methylation is one of these epigenetic modifications, which regulates genome function through processes that add or remove a methyl group to a specific site in DNA, potentially affecting gene transcription.

Animal studies have demonstrated that epigenetic changes from stress exposure can be passed on to the offspring. In the new study, Yehuda and colleagues examine these relationships for the first time in humans, with methylation of FKBP5, a stress-related gene that has been associated with PTSD and depression. The researchers examined blood

samples of 32 Holocaust survivors and 22 of their adult children, and Jewish parent-offspring control pairs for methylation of intron 7, a specific region within the FKBP5 gene.

The analysis revealed that both Holocaust survivors and their offspring show epigenetic changes at the same site of FKBP5 intron 7, but in the opposite direction; Holocaust survivors had 10% higher methylation than control parents, whereas Holocaust offspring had 7.7% lower methylation than control offspring.

"These observations suggest that parental trauma is a relevant contributor to offspring biology," said Yehuda.

John Krystal, Editor of *Biological Psychiatry*, noted that "the observation that the changes in parent and child are in opposing directions suggests that children of traumatized parents are not simply born with a PTSD-like biology. They may inherit traits that promote resilience as well as vulnerability."

The analysis was not able to disentangle the influence of parental gender. It was also unable to identify whether the effects in offspring resulted from trauma effects to the parental gametes or changes occurring to offspring during pregnancy or postnatally.

Childhood adversity is common in children with traumatized parents, so the researchers examined if the offspring's own childhood trauma played a role in the observed effect. "Interestingly, a relationship between methylation and reported childhood adversity was observed in the offspring, but at a different site within the same intronic region of the gene," said Yehuda.

According to the authors, their findings indicate that it may be possible to distinguish changes associated with early adverse experiences in

offspring from those associated with trauma in antecedent generations, suggesting the importance for clinicians to inquire about parental trauma in addition to personal trauma.

"This study raises important questions about the intergenerational transmission of traits from traumatized parents to their children," said Krystal. "The observation that the same genes might be affected in parents and children suggests that something specific, perhaps related to stress response, is being conveyed from parent to child."

More information: Rachel Yehuda et al, Holocaust Exposure Induced Intergenerational Effects on FKBP5 Methylation, *Biological Psychiatry* (2016). DOI: 10.1016/j.biopsych.2015.08.005

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