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## Trauma and stress, from child to adult

In some people, childhood trauma — such as physical or sexual abuse — can interact with genotype to increase the risk of conditions such as depression or post-traumatic stress disorder (PTSD) in adulthood, but the molecular mechanisms underlying such interactions remain unclear. Klengel *et al.* now show that a polymorphism in the FK506 binding protein 5 (*FKBP5*) gene interacts with early trauma to produce lasting epigenetic changes that increase the risk for such conditions.

Glucocorticoids are released in response to stress, and activation of the glucocorticoid receptor usually feeds back to reduce glucocorticoid release. *FKBP5* forms part of a negative-feedback loop that regulates glucocorticoid receptor activity, so changes in levels of *FKBP5* could perturb the stress response system and leave people vulnerable to conditions such as PTSD.

The authors identified a polymorphism in intron 2 of *FKBP5*. Adults who were homozygous or heterozygous for the A (risk) allele at this polymorphism rather than the G (protective) allele were more likely to suffer from PTSD — but only if they had suffered abuse as children.

The authors set out to identify the molecular underpinnings of this effect. They found that the risk allele was associated with an alteration in chromatin structure and increased transcription of *FKBP5*.

The resulting increase in *FKBP5* ‘tightens’ the negative-feedback loop that regulates glucocorticoid receptor activity, causing relative resistance to glucocorticoid receptor activation and an increased hormonal response to stress.

How do traumatic experiences in childhood interact with this risk allele? Glucocorticoid receptor activation — which is increased during traumatic experiences — is known to induce changes in DNA methylation. The authors found that CpG sites in intron 7 of *FKBP5* were less methylated in individuals carrying the risk allele who had a history of childhood abuse than in people with the protective allele or in risk allele carriers with no history of childhood trauma.

The results above were found using blood samples. To test whether similar mechanisms might be at work in neurons, the authors used a human hippocampal progenitor cell line. When these cells were exposed to the synthetic glucocorticoid dexamethasone during proliferation and differentiation, it led to marked demethylation in intron 7 of *FKBP5*. The decrease in methylation was stable over 20 days in steroid-free culture, supporting the idea that this epigenetic change could mediate lasting effects.

The downstream effects of demethylation in intron 7 of *FKBP5* included increased expression of

*FKBP5*, glucocorticoid receptor resistance and subsequent changes in the expression of genes controlled by the glucocorticoid system. In addition, *FKBP5* methylation was correlated with the volume of the right hippocampal head in humans, indicating that these processes can also lead to structural changes in the CNS.

The sensitivity of the risk allele to demethylation seems to be time-dependent. In culture, exposure of fully differentiated neurons to dexamethasone had no effect on methylation. Consistent with this, trauma that occurred during adulthood did not alter methylation in people carrying the risk allele. This leads to the idea of a sensitive period during which children with the risk allele are vulnerable to the induction of lasting epigenetic changes that predispose them to stress-associated disorders in adulthood.

These findings shed light on how the risk allele interacts with trauma to cause long-lasting changes. Further investigation of epigenetic changes should shed more light on how childhood experiences can shape development into adults and might also help to develop therapeutic avenues.

Rachel Jones

“ ... a polymorphism in the FK506 binding protein 5 (*FKBP5*) gene interacts with early trauma to produce lasting epigenetic changes ... ”

**ORIGINAL RESEARCH PAPER** Klengel, T. *et al.* Allele-specific *FKBP5* DNA demethylation mediates gene–childhood trauma interactions. *Nature Neurosci.* 2 Dec 2012 (doi:10.1038/nn.3275)