COMMENT

Epigenetic convergence in the rising tide of opioid overdose deaths

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A DEADLY CRISIS HIDDEN BEHIND THE PANDEMIC

The opioid epidemic is one of the most significant public health crises facing the US. Over 840,000 Americans have died from fatal overdoses where opioids were present as tracked by the CDC's National Vital Statistics System since 1999 (ref. [1]). Three successive opioid waves have resulted in overdose deaths: prescription opioids, heroin, and synthetic opioids like fentanyl [2]. Each transition to a more dangerous substance came from changes in accessibility among each opioid type [2]. For example, decreases in prescription opioid prescribing along with increases in the availability of heroin led to the second wave. In turn, fentanyl and its analogs pack an unpredictable and deadly punch. It can be produced more efficiently with less risk than heroin while maintaining heroin's powder form or could be pressed into pills like prescription opioids. Consumers may expect heroin and instead, consume a substance many times more potent [3]. COVID-19 and the dynamics surrounding it appear to have exacerbated the third wave. The CDC found a 38.4% increase in synthetic opioid deaths in the year ending in May 2020 compared with the year ending in June 2019. And, while COVID is most deadly in the elderly, accidental overdose deaths from opioids like fentanyl are inflicting those in the prime of their lives (Fig. 1).

The danger of fentanyl and its analogs makes understanding developmental pathways for opioid use disorder and opioid overdose, which are targetable with prevention or therapy, more imperative. Unfortunately, the relationship between these interlocking parts is poorly understood. Why do most opioid-exposed people maintain a healthy relationship with them, instead of progressing to an opioid use disorder? Why do others enter an inescapable downward spiral that eventually results in their death? What are the factors (genetic and epigenetic, nature and nurture) that might provide clues to long-term healing for individuals and society? A new paper sheds light on underlying gene regulatory networks relevant to these questions [4].

EPIDEMIC CLUES IN THE OVERDOSED EPIGENOME

In this report, a team lead by Olivia Corradin (MIT), Richard Sallari (Axiotl), Schahram Akbarian (Mt Sinai), Eric Johnson and Dana Hancock (RTI), Deborah Mash (Nova Southeastern) and Peter Scacheri (Case Western Reserve University) has sought to explore the dark regions of the genome where the majority of complex-trait-causing variation exist, and in the neurons of those who died overdosing on opioids [4]. They measured a chemical signature of genomic activity, a small grease-like modification (called acetylation) on the bead-like proteins that DNA wraps around (called histones) using a method that detects acetylation of lysine 27 on histone 3 genome-wide: chromatin immunoprecipitation followed by sequencing (H3K27ac ChIP-seq). This epigenomic flashlight allowed for the identification of differences in the prefrontal cortex (the decision-making center of the brain) of 51 individuals with high levels of opioid exposure, as compared to the prefrontal cortex of 51 sudden accidental deaths (Fig. 2). Using a series of complementary, rigorous, orthogonal, state-of-the-art computational approaches, the authors expertly uncover a highly concordant set of regions that are epigenetically dampened (hypoacetylated) in opioid-exposed neurons (and, very few significantly hyper-acetylated).

While the cases studied are from heroin overdoses, which have been in decline, the findings are even more today urgent amidst more deadly synthetic, modern opioids like fentanyl.

LIGHTNING ROD CORRELATIONS

While it is impossible, and ethically controversial, to attribute causality from these findings, three primary correlative findings highlight routes of potential innovation for the healthcare management of the opioid crisis:

1. The groups of hypoacetylated regulatory elements are enriched in genetic heritable risk for phenotypes that are epidemiologically linked to adverse childhood experiences (ACE), but not enriched for the Opioid Use Disorder genetic risk loci (as, OPRM1, the primary loci for opioid risk found among US Veterans, is not epigenetically different in the neurons despite overexposure to opioids). The fact that most heroin overdose deaths, for examples, occur most often in young people (ages 12–28) in harsh socio-economical conditions, rather than the older population, comports with the notion that early-life nurture is paramount in the prevention of these deaths.
2. The lack of correlation with depression in the top epigenomic plexi found here by Corradin, Sallari et al agrees with the only other epigenomic study of this kind we know of, which clearly separates suicides as a distinct group with no overlapping regulatory signatures to heroin overdose death, as measured in human neuronal cells from the prefrontal cortex [5].

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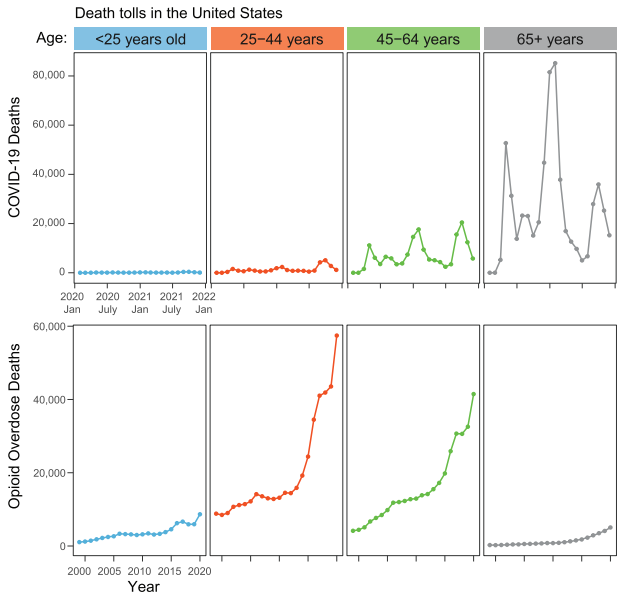

Fig. 1 Epidemic on the rise. Age inverted mortality trends among COVID-19 (top) and Opioid overdose deaths (below) in the United States. Data from https://wonder.cdc.gov/ and https://data.cdc.gov/browse.

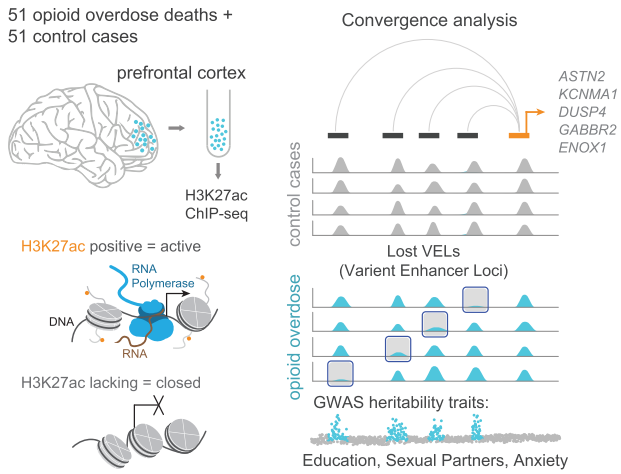

Fig. 2 Decisive epigenetic variation in opioid overdosed neurons. Measuring epigenomics of decision neurons from 51 overdose deaths, compared to 51 control cases, using H3K27ac and convergence analysis.

3. The genes with a loss-of-strength in their regulatory plexus (their 3D network of H3K27ac marked enhancer elements) are predominantly involved in known signaling pathways important for brain function (GABA signaling, MAPK signaling, and Potassium channels regulating neuronal excitability), offering new clues to treatment strategies beyond the controlled administration of opioids to fight addiction to opioids.

ADDICTED TO HOPE

We are hopeful that these data play a small but vital and science-backed role in allocating attention towards sources of systemic healing. In our view, the national and international hard conversations on lightning rod topics, such as this, will benefit from careful and deep analysis as presented in this new work.

Opioid overdose deaths also include substantial portions, but not all, of the "deaths of despair," identified by Case and Deaton [6, 7]. These deaths and related issues the authors identified appeared across multiple socio-demographic categories but were localized in white people without college educations [6, 7]. Understanding the epigenetic correlates may be essential to separating the societal from the genetic risk factors for opioid overdose death, and could enable the public health field to respond more effectively and save lives.

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AUTHOR CONTRIBUTIONS

BG and CH conceived of and co-wrote the manuscript. BG analyzed data and prepared figures.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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