

TRANSGENERATIONAL EFFECTS TO EXPLAIN THE RISE IN PREVALENCE OF MENTAL HEALTH DISORDERS

The prevalence of mental health disorders (MHD), such as ADHD, autism and mood disorders, has increased 2-3 fold during the last two decades in the USA, and probably in other high-income countries as well. Also rates of suicide and self-harming behavior in teenagers and young adults increased. In a paper in the March 2021 issue of the [Eur J Hum Genet, 29, 387–395 \(2021\)](#) Anthony Monaco, president of Tufts University in Medford, USA, provides a model to explain this important problem for society.

The model goes beyond traditional explanations based on DNA variants, because these only account for a fraction of the heritability and family clustering of MHD. The model includes transgenerational effects by three possible mechanisms, each supported by evidence from studies in rodents.

- 1) Epigenetic changes of the genome: in utero exposure to maternal stress or toxic agents leads to epigenetic changes of the fetal genome that affect long-term gene expression of the progeny.
- 2) Changes of the microbiome: an unhealthy vaginal microbiome has effects on health and behavior of male offspring, and affects gene expression in the hypothalamus.
- 3) Changes in the sperm content of non-coding RNAs, such as miRNAs and tRNAs by stress or poor diet have an effect on the behavior of the progeny, as brain micro-RNAs can be transmitted to the germ line and to the progeny by sperm.

There are indications that such mechanisms exist in humans as well. Environmental conditions that may play a role are substance use (drugs and alcohol), poor diet and obesity, as the rise in MHD coincides with increases in marijuana, cocaine, heroin, high sugar caffeinated soft drinks and processed foods rich in sugar and additives. This occurred 15-20 years before the rise of MHD, sufficient for a transgenerational effect to have taken place. Cooperatively, these environmental factors may have dysregulated reward pathways in basal ganglia, thereby sensitizing the brain to further rounds of exposure in the next generation.

Empirical support for this model comes from 11 neuropsychiatric and 3 metabolic disorders as they occur in 128,989 families in the USA (based on Insurance claims), for which it is shown that epigenetic effects explain much of the heritability. The good news is that epigenetic effects are reversible by reducing parental exposures to adverse environmental factors - a herculean effort for society but at the benefit of all.