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HOT TOPICS

Using the exposome to understand environmental contributors to psychiatric disorders

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Disease risk is governed by a complex interaction of hereditary and environmental factors. The modern revolution in genetic sequencing has dramatically expanded our knowledge of inherited genetic factors, while simultaneously promoting a silent bias toward overestimating the contribution of genetics to disease risk. The importance of environmental contributions to psychiatric disorders is illustrated by genetic studies that clearly cannot account for the majority of disease risk [1, 2]. We are now approaching a tipping point in the technology available to measure the sum total of all environmental exposures, referred to as the "exposome", which promises to represent the vast environmental space in equal proportion to the hereditary space [3].

A growing body of evidence links diverse elements of the environment to psychiatric disease. This includes environmental factors writ large, including local ecosystems, lifestyle choices, social factors, life experiences, and the physical environment; and the environment writ small, referring to exposures to toxic and non-toxic chemicals [3]. The vast majority of research on environmental exposures contributing to psychiatric disease focuses on individual candidate exposures and evaluates the effects relative to a small number of outcomes of a priori interest. While limited, this approach has yielded results of vast scientific importance. As an example, risk for autism and developmental delay has been linked to air pollution, heavy metals (such as lead), pesticides, phthalates, and polychlorinated biphenyls; medications such as valproic acid; and nutritional factors such as iron and folic acid [4].

The list of exposures related to psychiatric disease grows slowly every year, but the ability to rapidly expand this list is within our grasp. Advances in technology now allow us to measure all of the exposures of an individual simultaneously and relate those exposures to broader health outcomes, using a paradigm referred to as high-resolution exposomics. Using high-resolution mass spectrometry linked to a chromatographic separation technique, it is possible to measure tens of thousands of chemical signatures from the same sample, representing both endogenous metabolites and exogenous exposures. This can be done using clinical or pre-clinical samples of any tissue, though blood, saliva and urine are the most well validated. Additional efforts are underway to develop multi-omics approaches using both genomic and exposomic data simultaneously to assess gene-by-environment interactions at scale [5].

The "sister" technique, high-resolution metabolomics, uses similar technology (typically with gas chromatography) to represent all endogenous metabolites measurable in the target tissue. Like exposomics, high-resolution metabolomics can provide a metabolism-wide representation of the effects of a single exposure (or an environmentally relevant mixture) in an animal model, and can be used to generate both temporal and dose-related information.

The opportunity to surpass "candidate exposure" studies has arisen at a time when the weakness of conceptually similar "candidate gene" approaches is becoming apparent. Nonetheless, major challenges remain in the field of exposomics. High-resolution exposomics provides such depth of detection that many chemical signatures have yet to be identified and annotated [3]. Another major challenge is the development of network-based computational frameworks for making sense of seemingly unrelated chemical risks; understanding chemical interactions and mixtures; and accounting for metabolism.

Applications of newly developed exposomics approaches to psychiatric disease risk remain rare, but under consideration [6], and represent low-hanging fruit for the field. Just as genome-wide studies revolutionized the study of the genetic inheritance of disease risk, exposure-wide studies, using exposome-based methods, are positioned to revolutionize the study of environmental contributors to disease risk.

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AUTHOR CONTRIBUTIONS

JPB and GWM contributed equally to this work.

ADDITIONAL INFORMATION

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