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Gene-Environment Interplay and Epigenetic Processes

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Introduction

By uncovering how genes and the environment affect each other at the molecular level, epigenetics promises to unveil how individual susceptibility and social conditions work together to affect individual differences in development, behaviour and child well-being. There is increasing evidence demonstrating that interactions between genetic predispositions and early life adversity are related to the emergence of neurodevelopmental health issues.

This report describes different domains of gene-environment interplay and reviews recent research findings from observational and population studies in humans, and experimental studies in monkeys.

Subject

There are at least three categories of processes where interactions between genes/gene expression and the environment lead to differences in development trajectories that affect mental health and well-being. First, there is a correlation between genes and the environment,

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where a child has a genetic predisposition (an increased chance) of selecting, altering or generating categories of experience, for example, a child with behavioural inhibitions has a tendency to choose less challenging or less intensive social environments. Second, genes and the environment can affect each other bidirectionally. For example, there are cases where genetic variations only become apparent in the presence of specific environmental conditions, and alternatively, there are examples where environmental influences are revealed only among individuals carrying a particular genetic variant (genotype). The third category of interaction involves epigenetic processes where environmental signals mark or tag DNA and in some cases this can alter gene transcription and expression. These processes are discussed in greater detail in the first article of this chapter.[2]

The exploration of these three domains of gene-environment interplay has become a prolific and engaging area of biomedical and social science research that promises to illuminate one of the deepest mysteries of human experience — how individual susceptibility and social conditions work together at the behavioural, physiologic, neural, cellular and molecular levels to initiate and sustain individual differences in development, behaviour and health, in some cases lead to disorders.

Problem

Many molecular mechanisms control gene expression. Groundbreaking research seeks to reveal how epigenetics is involved in the interplay between genes/gene expression and the environment and the consequences for brain development, behaviour and well-being.

Research Context

Though suspected for a long time, it was only about a decade ago that reports appeared showing that epigenetic processes are associated with long-term human developmental and health outcomes. Studies in 2002 and 2003 revealed statistical links between early environmental conditions such as child maltreatment and stressful life events and the genetic variant one carries to predict antisocial behaviour and depression and the risk of suicide.[3,4]

As the body of research has grown in size and data from a number of studies have been reviewed together in meta-analyses, researchers have found strong evidence for these interactions. For example, a 2010 review of more than 40 studies about gene-environment interactions involving the serotonin transporter gene revealed strong links to sensitivity towards negative and stressful

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environments,[5] and a 2011 review of 54 studies found strong evidence that the serotonin transporter gene 5HTTLPR is involved in moderating the association between stress and depression.[6]

Recent Research Results

New evidence continues to build, demonstrating that environmental interactions with genes have an impact on early human neurodevelopment.

Observational Research

One group of researchers recently reported an interaction between mothers' dopamine receptor gene, DRD4, and reports of prenatal stress with predicting their children's risk for developing antisocial outcomes such as conduct disorder or oppositional defiant disorder in early adolescence.[7] In another study, researchers with the Bucharest Early Intervention Project (http://www.bucharestearlyinterventionproject.org/) identified a gene-environment interaction in children who remained institutionalized and were carriers of gene variants responsible for maintaining appropriate levels of two brain transmitters, dopamine and norepinephrine. Depletion of these neurotransmitters has been implicated in the risk for major depression. In another study, the early adversity of mothers as measured using a childhood trauma questionnaire interacted with the genetic variant they carried in the PRKG1 gene to affect maternal sensitivity to her infant. One variant buffered these mothers from earlier adversity while the other did not. This gene by environment interaction was replicated in two cohorts.[8] Finally, researchers examined data from twins in the Early Childhood Longitudinal Study (https://nces.ed.gov/ecls/) and found that genetic variation contributed in cognitive ability but was dependent on reciprocal, developmentally moderated interactions between children and their environment, and that children who were being raised in higher socioeconomic status homes were showing significantly higher scores by the age of 2 years.

In studies involving rhesus macaques, researchers demonstrated that early rearing conditions with either mother or peer-related groups interacted with the serotonin transporter gene. That interaction had an observable, predictable impact on the manufacture of stress hormones during times of separation stress.[9] Further, the interaction appeared to apply even among normal monkeys, where social dominance status during development worked together with the serotonin transporter gene and could predict the timing of sexual maturation: subordinate female monkeys

who carried at least one copy of the altered promoter gene had significant delays in sexual maturation.[10]

Epigenetic processes at the population level

One of the most intriguing recent discoveries is that epigenetic processes can influence the development of specific populations of people. For example, the maltreatment of children has been linked to faulty regulation of the hypothalamic-pituitary-adrenal (HPA) axis,[11] a complex set of interactions between endocrine glands that produce hormones to regulate many body processes including stress, mood, sexuality, digestion, the immune system and energy storage, to increased inflammatory signaling[12] and long-term changes in stress-responsive neural structures.[13]

A study of over 200 newborns in Singapore found that there were over 1,400 genomic regions with wide variation in the state of epigenetic tagging across individuals, and that 75% of the measured variability in DNA methylation arose from genetic variants in interaction with environmental factor which included for example, maternal smoking, maternal depression, maternal BMI, infant birth weight and gestational age. Genetic variation alone accounted for 25% of the variation in methylation. Thus, there is a complex relationship between variation in methylation, the DNA sequence and environmental exposures.[14]

Finally, researchers have recently demonstrated that epigenetic profiles in human populations are highly divergent, involving differences in frequencies of underlying genetic codes and complex gene-environment interactions. One series of studies examined over 14,000 genes in 180 different cell lines from European and African samples. Researchers found population-level differences in DNA methylation in over one-third of the genes and that most of these differences were attributable to differences in underlying numbers of gene variants.[15] Other researchers have found similar epigenetic differences between populations.[16,17,18]

Research Gaps

To date, causal evidence about the relationship between genes and the environment is lacking in human populations. The sheer number of genes and environmental variables and their interactions poses a significant challenge for experimental research design in humans. Causal relationships between candidate DNA variants and their interactions with epigenetic modifications under adverse environmental conditions can be tested using animal models.

In the future, the use of computers to perform higher-level mathematical modeling techniques to search for gene-environment interactions is expected to overcome this challenge and advance the field. Risk scores associated with developmental phenotypes,[19] the observable characteristics and traits in development, and mathematical models of genome-wide association studies could one-day offer more answers than single searches can provide today.[20] The way forward will examine how many genes work together as a network to add or multiply the effects that lead to developmental disorders.[21]

Conclusions

Gene-environment interplay has emerged as a promising point of origin in studies of divergent developmental trajectories and the emergence of maladaptive outcomes including mental disorders. While there are many molecular mechanisms that control gene expression, research examining epigenetic processes is providing a groundbreaking look at how and under what conditions the intersection of genes/gene expression and the environment arise.

Implications

Early life adversity or enrichment has far reaching effects across the lifespan. Gene-environment interactions between specific gene variants and risk-engendering early social environments may be linked to differences in epigenetic processes, explaining variation among individuals in the expression of genes linked to neurodevelopmental disorders. In the future, changes in epigenetic marks in response to an intervention could also provide useful biomarkers for evaluation of the effectiveness of the intervention.

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