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Psychiatric practice can effectively help our patients overcome their genetically and neurobiologically driven maladaptive behavior

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Is anatomy destiny? Not according to GxE!

The long-held dogma that “anatomy is destiny” is fraying at the edges. The traditional nature vs nurture debate has also undergone a major transformation into a gene-by-environment interaction, abbreviated as GxE in the medical literature.^{1,2} This is as true for psychiatric brain disorders as for any other medical illness.

The pessimistic determinism of “anatomy is destiny” has given way to a much more optimistic perspective, especially for the most plastic of all organs, the human brain. While genes are essential to construct one’s anatomy, environmental factors can significantly modulate gene expression. A person’s life experiences, good or bad, can wield a lasting influence on one’s brain structure and function, often transcending what is coded by the genome. For the mind, its thoughts, emotions, and cognition, the neurogenetic “tyranny” can be curbed or modified by one’s experiences. This epigenetic process is alive and well and known to be mediated by DNA methylation and histone modifications.

Consider the following examples of how genes are not the sole determinants of one’s mental health:

- A landmark study conducted in New Zealand³ followed a cohort of 847 individuals from age 3 to 26. Researchers recorded stressful life

events for each participant, including romantic breakups, grief, medical illness, or employment problems, between age 21 and 26. Participants were evaluated for depressive episodes and hospitalizations and their genes tested for whether each individual carried the short (S) or long (L) allele of the serotonin transporter (5-HTT) gene. They found that when life stresses occurred, the probability of depression was much higher among the subgroup who were SS homozygous than among the LL homozygous subgroup. Thus, the genetic vulnerability to depression did not manifest itself unless adverse environmental events occurred. This is a classic example of GxE interaction, where genes alone are insufficient to produce a psychiatric disorder without environmental events interacting with them and triggering the psychopathology.

- In the same cohort described above, investigators showed that some children who were abused at an early age developed antisocial behavior as adults, while others did not.⁴ They discovered that a high expression of a polymorphism in the gene that codes for monoamine oxidase A had a protective effect that decreased the likelihood of developing antisocial traits in children who experienced trauma. In this case, the life experience failed to worsen a child’s behavior in the presence of elevated levels of a genetically determined protective enzyme.

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• Schizophrenia is a heterogeneous neurodevelopmental syndrome caused by numerous genetic factors (risk genes, copy number variants, and de novo mutations) and a wide variety of perinatal complications. Concordance for schizophrenia in monozygotic twins who have identical genes is only 50%, not 100% as would be expected.⁵ Obviously, nongenetic factors during fetal life must play a role in disrupting the neurodevelopment of the affected twin, but not in the healthy twin. Examples of such factors may include differential distribution of blood during fetal life, leading to low birthweight and hypoplastic brain volume in the affected twin. It may also be due to labor complications, where one twin has an uneventful vaginal delivery while the other experiences hypoxia, a brain insult, due to a complicated breech delivery. Thus, despite having the same genes, the postnatal outcome in a discordant monozygotic twin pair diverges dramatically.

• A recent study⁶ identified somatic mutations in monozygotic twins discordant for psychiatric disorders, including schizophrenia and delusional disorder. Such somatic mutations have also been found in Van der Woude syndrome, which includes cleft palate. However, skillful surgeons can repair the cleft palate and allow the affected twin to have a normal facial appearance and oral functions, offsetting the abnormal genetic code.

• A monozygotic twin pair (one of whom was a patient of mine) born to a mother with bipolar disorder and adopted at birth by different families developed bipolar disorder due to genetic transmission, but eventually had very different outcomes. One twin was promptly and successfully treated with lithium at the first manic episode and

became a successful teacher and author, while his twin did not receive treatment, became addicted to drugs, was repeatedly incarcerated for assaultive behavior, and later completed suicide at a young age. The appropriate environment and experiences of a person who inherits a psychiatric disorder can dramatically alter the prognosis for the better.

The GxE neurobiological equation is a central feature in many of our patients. As clinicians, we can modulate the patient's environment by providing timely therapeutic biopsychosocial interventions to our patient to catalyze the GxE equation and veer it towards health, resilience, and wellness. Psychiatric practice can effectively help our patients overcome their genetically and neurobiologically driven maladaptive behavior and enable them to recover from the ravages of neuropsychiatric illness. Thus, psychiatric care represents the ultimate "E" that can interact with and modulate the "G" and effectively demonstrate that anatomy is not destiny.

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