Genes are not our destiny: the somatic epitype bridges between the genotype and the phenotype

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Recent advances in human genetics research suggest a strong role of gene and environmental interaction in human behaviour and disorders. In this context, our laboratory found the July 2006 Perspective by Caspi and Moffitt¹ to be of great interest. They provided a succinct overview of useful interaction between neuroscience and genetic epidemiology that was well illustrated. They were also on the mark regarding experimental and procedural practices that would improve the utility of combining genetic/epidemiological and neuroscience approaches. As a theoretical overview, their paper was excellent. However, it relegated gene-environment interaction to a “black box of biology” and presumed that genetic alleles were not subject to environmental modification — that a gene’s contribution towards a specific neurobiological disorder is exclusively due to its primary DNA sequence (including the primary sequence of a gene’s promoter region). Pre-extant primary gene sequence variation provides a factor in addition to environment and a nebulous ‘neural substrate reactivity’ that influence the presence or degree of a disorder (FIG. 1a).

Caspi and Moffitt did not mention physical mechanisms to explore, perhaps owing to space constraints. We propose that primary gene sequence variation is often not the immediate operator in neurobiological pathology. Instead, environment acts on the genetic substrate, producing a ‘somatic epitype’. It would be this somatic epitype that directly provides gene-based influence on neuropathological etiology. Somatic epitypes are a form of epigenotype that arises through environmental influences on a genome in a single lifetime rather than the more familiar epigenetic inheritance^{2,3}. These somatic epitypes would correspond to physical alterations in gene promoters, be that through (hypo)methylation, chromatin structure or oxidative damage (as oxo-d8-guanosine). This could be instilled on the underlying gene sequence by conditions *in utero*³, by maternal behavior⁴, and/or by maternal nutrition⁵ or post-natal environmental effects such as nutrition or transient exposure to heavy metals such as lead⁶. One such example of a somatic epitype could potentially be found in the *SP1* gene, which has been shown to be perturbed in a latent associated early-life regulation (LEARn) fashion after transient developmental exposure to lead⁷. A LEARN somatic epitype would not manifest until well after exposure to an environmental effector had ended. In the case of *SP1*, the potentially associated neurobiological disorder would be Alzheimer’s disease⁷.

Caspi and Moffitt express the interaction of genes and environment as a black box described by ‘ $G \times E \rightarrow D$ ’ (gene and environment produce disorder). We propose that, for many neurobiological disorders, taking the lid off that box would reveal ‘ $E \times G \rightarrow G_{SE}, G_{SE} \rightarrow D$ ’ (environment operates on gene to produce somatic epitype, somatic epitype expresses as disorder). Variations in gene expression levels due to somatic epitype would essentially be Caspi and Moffitt’s ‘neural substrate reactivity’ (FIG. 1b). Application of our model, of course, would not presume a one $-G_{SE}$ to one disorder relationship, as a given disorder would probably depend on perturbation of the expression levels of several genes, and the difference between variation and disorder could still be at least to some extent environmentally (for example, culturally) defined.

If the specific mechanism of the somatic epitype is related to methylation state, this model also suggests potential therapeutic adjuncts for the restoration of a healthy somatic epitype. Such adjuncts could amount to dietary modification, as suggested by recent report of reversal of presenilin 1 upregulation by the dietary administration of apple juice concentrate⁸. In

conclusion, we certainly do not dispute Caspi and Moffitt's opinion that neuroscience/psychiatry and molecular biology will both benefit from close collaboration. Instead, we propose a mechanism to test the theoretical model they have presented, that is, the somatic epitype is the means whereby genes only are not our destiny.

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Figure 1 | **The somatic epitype as a candidate ‘neural substrate’.** **a** | Caspi and Moffitt's ‘black box’ model¹, wherein gene (G) and environment (E) interact in some unknown fashion in a neural substrate (N) to produce a disorder (D). **b** | A proposal that the somatic epitype is the content of their black box, and environment acts upon a gene to produce a somatic epitype (G_{SE}). Changes in gene expression levels would be the neural substrate that is manifest as a disorder.

A

1. Disorder links to neural substrate N
2. Environment effects neural substrate N
3. Genotype effects neural substrate N

B

1. Disorder has indeterminate linkage to certain genes (G)
2. Environment interacts with gene sequences to produce somatic epitype (G_{SE})
3. Somatic epitype alters gene expression levels, corresponding to disordered state