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Commentary

Time to Admit Genes and Epigenetics are Indeed the Blueprint for a Rewardful Life Whereby the Organism Controls the Genome

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An article in *BioEssays* by Oxford biologist Denis Noble declared a Kuhnian "paradigm shift" away from the concept of junk DNA, suggesting that we need to eliminate the notion that genes only make proteins because our genome contains many "RNA genes that produce RNAs that induce vital functions". Loudly, another article by Noble, this time in *Nature,* is calling for a major "rethink" of biology by charging that "*It's time to admit that genes are not the blueprint for life*," and criticizing the oversimplified and outdated view of biology often presented to the public. Noble emphasizes that while genes are important for life, it's the "*organism that controls the genome*!" [1].

It is indeed interesting that while Philip Ball in his book *How Life Works* [2] suggests that albeit there some truth in thinking about the metaphor *"our brain is like a machine/computer"*, he also calls for the exquisite idea that life might as well be *"sprinkled with invisible magic" but reality "is far more interesting and wonderful."* In this vein, Noble wisely suggests that there are a number of mysteries regarding understanding protein interactions and structure function. Noble argues that biological systems that are more complex than often appreciated are "intrinsically disordered proteins" (IDPs) - proteins that don't have a stable three-dimensional shape. However, Venema [3] cites intrinsically disordered proteins (IDPs), noting they "*do not need to be stably folded in order to function"* and therefore represent a type of protein with sequences that are less tightly constrained and are presumably therefore easier to evolve. In fact, IDPs can adopt different three-dimensional structures, but that isn't because their shape doesn't matter but rather because they can switch from one shape to another - like miniature transformers - to perform different functions.

Obviously, the right amino-acid sequences perform their component functions, each of which serves the high-level function of the whole organism. From an evolutionary perspective we must consider, as did Noble, the concept that -"*Evolution is often regarded as "a slow affair of letting random mutations change one amino acid for another and seeing what effect it produces". But in fact, proteins are typically made up of several sections called modules - reshuffling, duplicating and tinkering with these modules is a common way to*

produce a useful new protein". Noble's vision of biology is one where dogma is discarded, new ideas are considered, agency and purpose are acknowledged, cells are *more* complex than computers and machines, proteins are like miniature transformers, and organisms control their genomes, is highly compatible with intelligent design - certainly far more compatible than the biological thinking of the past hundred years. This means biology is moving in the right direction.

Noble correctly points out that stochasticity is harnessed by organisms to generate functionality. Whereas randomness does not, therefore, necessarily imply lack of function or 'blind chance' at higher levels. In this respect, biology must resemble physics in generating order from disorder. Interestingly, this fact is contrary to Schrödinger's idea of biology generating phenotypic order from *molecular*-level order, which inspired the central dogma of molecular biology. We now know that this includes the genome, which is controlled by patterns of transcription factors and various epigenetic and reorganization mechanisms. So, one possibility may evolve whereby the agent (an unknown force) induces a potential new purpose for a specific protein to have futuristic importance. These processes can occur in response to environmental stress so that the genome becomes 'a highly sensitive organ of the cell'. [4]. Organisms have evolved to be able to cope with many variations at the molecular level. Organisms also make use of physical processes in evolution and development when it is possible to arrive at functional development without the necessity to store all information in DNA sequences.

Currently, hundreds of millions of Americans have indulged in the use of illicit psychoactive and addictive drugs in their life. We must ask then, who are the people that could just say NO? When almost half of the US population have indulged in illegal drug practices, when our presidential candidates are forced to dodge the tricky question of their past history involving illegal drug use, and when almost every American has sloshed down a martini or two in their lifetime, there must be a reason, there must be a need, there must be a natural response for humans to imbibe at such high rates. Why do millions have this innate drive in the face of putting themselves in harm's way? Why are millions paying the price of their indiscretions in our jails, in hospitals, in wheelchairs and lying dead in our cemeteries?

What price must we pay for pleasure-seeking or just plain getting "HIGH"? Maybe the answer lies within our brains. Maybe it is in our genome? Utilization of the candidate vs the common variant approach may be parsimonious as it relates to unraveling the addiction riddle. Previously Blum., *et al*. [5]. discussed evidence, theories, and conjecture about the "High Mind" and its relationship to evolutionary genetics and drug-seeking behavior as impacted by genetic polymorphisms. They considered the meaning of findings in genetic research including an exploration of the candidate vs the common variant approach to addiction, epigenetics, genetic memory, and the genotype-phenotype problem. In fact, Ball suggested there is the possibility, as Comings also speculated,[2] that there is a chance that the drd2 A1 allele will increase at the rate of 1:25 every decade. This rise in the now minor allele of the *drd2* receptor gene (*drd2A1)* could involve not just the DNA but the profound behavioral epigenetic effects as previously discussed [6].

As pointed out by Noble [7], development and evolution differ radically from that of neo-Darwinism with its emphasis on blind chance as the origin of variation. These observations derive from and reinforce the principle of biological relativity, which holds that there is no privileged level of causation. Accordingly, the prime purpose of this editorial, prepared by a team of scientists and clinicians comprising the RDS Consorium, is to help clarify Noble's profoundly thoughtful statements regarding the role of DNA (genome) in terms of providing the inescapable code of life's blueprint, and to apply them in the context of substance addiction. To this end a brief history of the famous formula P = G + E seems instructive. This formula focuses on gene-environment interactions, often abbreviated "G × E" and pronounced "G-by-E." G × Es are interaction effects, distinct from genetic main effects.

The presence of a G × E implies that the effect of an environmental variable (on phenotype) depends on genotype and vice versa and that the effect of genotype (on phenotype) depends on the environment. G × E effects have been studied in psychiatry and psychology for decades using a variety of methodological techniques [8]. It is noteworthy that a word search in PUBMED using *"role of environment vs DNA in life"* from the 60s to 2000 showed no results. In 2010 there were only two papers that discussed this important issue; in 2020 only eight and from 2021 to 2024 there were approximately 30 total. However, if you switch

"environment" for "epigenetics" - "role of epigenetics vs DNA psychiatry" - the result is remarkably different with environment = 51 and epigenetics = 86 (assessed on 10-6-24). Certainly, we are very cognizant of the relatively new field related to epigenomics and its powerful impact in the field of not only generalized medicine but in the understanding that the combination of both our DNA and epigenetic chromo-chemistry on expression of genes and proteins thereof especially in disease.

In fact, there is evidence for non-DNA inheritance up to six generations [9]. Our point here is to drive home the idea that while epigenetics as we now know it today has been around for probably 400 million years, and only in modern times have we developed a neurogenetic language to help explain the important impact of environmentally induced histone modification with either methylation (reduce gene expression) or acetylation (enhance gene expression) depending on type of environmental stimuli -abusive or positive, and that provides the miraculous hereditary intelligence map.

Further, the discovery that the genome is not isolated from the soma and the environment and that there is no barrier preventing somatic characteristics from being transmitted to the germline supports Darwin's pangenetic thinking [10,11].

Indeed, there is the question posed by Noble's group whereby relating genotypes to phenotypes is problematic not only owing to the extreme complexity of the interactions between genes, proteins, and high-level physiological functions but also because the paradigms for genetic causality in biological systems are seriously confused. One major truth is that because of the powerful impact of environmentally induced epigenetic alterations in DNA expression, one's given DNA at birth no longer is considered the "end all." Instead of the nature of DNA sequences guaranteeing primacy in causation compared to non-DNA inheritance, it is in real life that the combination of these multi-factors is explained by downward causation [12-14].

Along these lines, Noble penned a simplified but coherent reductionist theorem to encapsulate his work-*"Successful biological analysis requires that we understand the functional interactions between key components of cells, organs, and systems, and how these interactions change in disease. This information resides neither in the genome nor in the individual proteins that genes encode. It lies at the level of protein interactions within the context of sub-cellular, cellular, tissue, organ and system structures"* [15].

The idea that processing DNA antecedents for any disease does not mean that one is doomed and guaranteed to succumb to the disease in question, especially so for genes related to mental health. Genetic studies have shown that obesity risk is heritable and that, of the many common variants now associated with body mass index, those in an intron of the fat mass and obesity-associated (FTO) gene have the largest effect. The size of the UK Biobank, and its joint measurement of genetic, anthropometric, and lifestyle variables, offers an unprecedented opportunity to assess gene-by-environment interactions in a way that accounts for the dependence between different factors. We can jointly examine the evidence for interactions between FTO (rs1421085) and various lifestyle and environmental factors. Young., *et al*. [16] report interactions between the FTO variant and each of frequency of alcohol consumption (P = 3.0 × 10(-4)); deviations from mean sleep duration (P = 8.0 × 10 (-4)); overall diet (P = 5.0 × 10 (-6)), including added salt (P = 1.2 × 10(-3)); and physical activity (P = 3.1 × 10 (-4)), These results show that FTO gene variant modifies these obesogenic related factors. Another study [17] confirmed the association between body weight and the FTO rs9939609 polymorphism. Interestingly, their results showed that, although at baseline the A allele was associated with higher body weight, after 3 years of nutritional intervention with a Mediterranean-style diet, A-allele carriers had lower body weight gain than wild-type subjects.

Apart from the pressing question of differentiating for example, psychiatric disorders from the "normality" to which treatment should regress, a further critical issue is the discrimination between specific psychiatric disorders themselves, and their overall classification. Our group and others have argued that the brain is not carved out so precisely as represented in DSM-5 [18-22]. Refining diagnostic criteria is a far from simple process and is still ongoing as embodied by successive World Health Organization coordinated editions of, (1) the ICD, mainly for general practitioners and educational use, and (2) of the American Psychiatry Association-sponsored DSM, mainly for psychiatric specialists and clinical research [18-24].

In fact, some might provocatively debate whether there is an absolute need for a diagnostic system by categories of disorder,

since a standardized diagnosis can become disconnected from underlying mechanisms in grouping together either too many (or too few) individual cases. For example, the over-extension of the notion of schizophrenia in North America during the 1950s and 1960s eventually compromised its significance, and it is possible that an analogous problem with bipolar diagnosis in childhood is causing similar problems today. Nonetheless, this does not invalidate the approach, but rather incites greater care and thinking into the discrimination of diagnostic groups, as attempted by DSM-5.[25] We must ask whether the concept of Reward Deficiency Syndrome (RDS) or even just reward deficiency is considered as an umbrella term to help us understand the real functioning of the brain. In this regard, there are 1,591 articles listed in Pubmed (retrieved 10/24/24). The RDSconsortium previously proposed that the concept of "pre-addiction" is indeed RDS requiring [25].

Moreover, at least initially, a diagnosis is less of a fact, rather more of a hypothesis awaiting proof of concept before final confirmation. In addition, categorizing disorders (and treatments) best can be important for assessing the scale of psychiatric disorders in society, for evaluating the utility of treatments for reimbursement, and for communicating with patients. However, we must pause and consider an alternative diagnostic approach using a genetic approach to help identify early addiction risk and potential severity such as observed in a series of recent experiments [25-35].

Concomitantly with this ongoing discussion as to how best to clinically classify psychiatric disorders, and especially the overall laudable goal to reach "happiness", a parallel, equally important, and more research-driven process is underway to better understand their neurobiological substrates [36,37].

Conclusion

It is indeed remarkable that since the discovery of the double helix to the mapping of the human genome, investigations of the complex workings of our genetic blueprint emphasize well-being as an ultimate goal of *homo sapiens.* This biological imperative may reside in the fundamental interaction between one's DNA (genes) and the expression of translational protein processing via the mRNA (epigenetics).

In fact, one's behavior influences genes and environmentally induced epigenetic impacts extending up to 6 generations. (CONCLUSION) The emergence of this new biology, thanks to the outstanding efforts of Denis Noble and Philip Ball, has challenged the past dogma whereby genes dominate the environment. Evidence is now rapidly emerging, showing that both DNA and epigenetics contribute to the overall phenotypic variance, suggesting that the organism, rather than the genome alone, is in control. Current dogma suggests that instead of the genome controlling an organism, it is the opposite, especially for rewarding events, whereby genetic inborne unique polymorphisms are not the controlling factor, but it is the interactiveness with the environment and subsequent epigenetic chemistry that controls the endophenotype.

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Author Contribution

The initial concept was developed by ERB and KB. The initial manuscript was penned by KB. All co-authors contributed significantly by providing edits to the manuscript followed by final approval.

Conflict of Interest

Dr. Kenneth Blum reports royalties from and discloses many pending USA and foreign patents on GARS and KB220 variants licensed to Synaptamine. The authors report no other conflicts of interest in this work.

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