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Brief Report

An enhanced understanding of genotype-phenotype variation is provided by the Praxitype

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ABSTRACT

There is a need for an understanding of the genomic reality that realizes a connector between the genotype and the phenotype by addressing HOW the genotype actually manifests as the phenotype, as a function of the locus or the allele, mutated, variant or wildtype. That understanding is encompassed by the notion of the PRAXITYPE, which assembles and presents the available answers to the HOW!

Keywords
Praxitype; Genotype-Phenotype variation; Genome variation; Neurological disorders; Neurofibromatosis type 1 (NF1).

INTRODUCTION

It is hard to imagine anything more complicated than the organization and function of the mammalian-especially human-nervous system. For a while it seemed simplified by single gene mutations being the basis for complex neurological disorders: specify the mutated gene and "everything was accounted for." A bit more thought and experience made it clear that this was an over-simplification: HOW the mutant gene was expressed was at least as much of a factor as WHICH gene was mutated. Obviously, there were myriad superimposed factors, especially genetic ones. In short, the HOW of gene expression is largely explained by epigenetic factors, such as microRNA, the "availability" of the gene (mutant or otherwise), regulatory biochemical networks (e.g., Ras), etc.

That is, we no longer can rely on the genotype, the "what" of pathogenesis: we also need insight into the "How." I have specified the latter as the Praxitype! Thus, when we look to assess, to evaluate neurological disorders from a genetic vantage point-that is, in terms of "genome variation"- there is more to it than the Genotype, the allele at a specific genetic locus. What follows is an introduction to what is beyond the genotype that addresses genome variation and how genes are fully manifest, critical for understanding genetic neurological disorders!

DISCUSSION

The phrase, "Genome Variation," implies, if not declares, that the relationship of the details regarding an individual's genome (i.e., genotype) to the details of that individual's combination of traits (i.e., phenotype) is variable, sometimes to the point of being confusing or even incomprehensible. Said more succinctly, genotype-phenotype correlations are not as fixed or predetermined as they are usually presumed to be. That is, knowing the genotype, whether in terms of a single locus or a combination of loci, is unlikely on its own specify the derivative phenotype. At the least, one would wonder whether another factor or set of factors was at play. I say there is another factor, and that it is the matter of how the genotype is manifest, how the gene (locus or allele) is put into practice. How the gene is literally put into practice can be referred to as the praxitype, respecting the same etymology of the terms, genotype and phenotype, as I have proposed and employed several times before.[1-5]

In an earlier era, we naively presumed that knowledge of the genotype (γ) readily revealed the phenotype (φ), and vice versa. It was that simple–there was no interloper: γ and φ supposedly just revealed each other. For example, homozygotic loss of the phenylalanine hydroxylase gene translated to phenylketonuria; and heterozygosity for a Huntingtin gene mutation translated to

Huntington's disease. Conversely, the clinical presence of Sickle Cell Anemia or of Neurofibromatosis type 1 (NF1) translated to homozygosity for certain β-hemoglobin gene mutations and heterozygosity for an NF1 gene mutation, respectively. Such translations were both expected and sufficient.

However, on multiple levels it has gotten much, much more sophisticated and complicated. Details of the genotype just aren't enough to reveal or account for the phenotype. We need to know additional details–the obvious and still undiscovered details of how the genotype actually translates to the phenotype. What does that segment of deoxyribonucleic acid (DNA) actually do and what is done to it and its products? How do the elements of the phenotype initiate and progress in terms of the DNA, its transcribed messenger ribonucleic acid (mRNA), and the latter's protein translation? How are other gene loci involved? How does the genotype become the phenotype (γ→φ)? The realistic answers utilizes an intermediary, the praxitype (π). The answer(s) to "How?" is a matter of γ→π→φ.

A.R. Gehrke and his co-workers, in a March 2019 publication in Science,[6] directed themselves at the genetic "regulatory landscape of whole body regeneration" of acoels, which "regulatory landscape" the authors consistently and satisfyingly referred to as the "gene regulatory network" (GRN). I presume that the GRN, so considered, is overlapping with the notion of the Interactome, as used by other authors,[7-10] and contributes to the notion of the praxitype, as I have used and promulgated it (vide supra). Their efforts and mine, individual or combined, promote the same notion–it is not merely the genotype, but how a gene (locus, allele, mutant, etc.) is put into practice; how it is manifest as a phenotype. Or, more precisely, how the genotype is put into practice as a function of the multiple regulatory elements impinging on or blatantly determining the gene's/allele's expression.

In order to understand, to comprehend, to expand genetic regulation, that is, genetic finesse, there must be an interloper between the genotype and its variable phenotypes. That interloper is the praxitype! In order to discuss meaningfully the relationships of γ and φ, there must be categorical appreciation and articulation of the π. Resorting to the praxitype will (respecting it's same logic and same etymology as the phrases/concepts, genotype and phenotype) become increasingly suitable and necessary for understanding and broadcasting the relations between a locus or allele and its consequences. In my own work on the disorder, Neurofibromatosis 1 (NF1), over some 47-years,[11,12] my regular, intense utilization of the praxitype paradigm has magnified for me the veracity and practicality of this logic. The NF1 gene's myriad varieties of causative germinal intragenic mutations or whole-gene-deletions have made it imperative that we uniformly and systematically acknowledge and exploit the interloper that we had otherwise been pursuing piecemeal and inconsistently as the interactome or "gene regulatory network." Allelic interactions, pseudogenes, the timing and intensity of chromatin methylation, micro-RNAs, protein and mRNA degradation, and other aspects of how the genetic code is translated are the substance of the praxitype and our understanding and implementing genetic knowledge. I encourage–downright urge, even coerce–our genetic colleagues and acolytes strongly to consider this approach. Just do it–incorporate this jargon and concept into your writing and watch the salutary impact.

In my introduction to the substance of neurologic diseases, I emphasized their complexity and How this complexity unfolds. Likewise, in my acknowledgment of my involvement with NF1, I emphasized NF1's complexity and how it unfolds. There can be no greater consideration of the complexity and challenge relevant to the details of neurological disease and the Praxitype than the unfolding of NF1's phenotype.[10,13-15] Von Recklinghausen disease, or NF1, is likely the key to elucidation of the Praxitype. Thus, increasingly there is resort to concerns about How the NF1 phenotype becomes manifest. How does one disorder account for cognitive compromise, skeletal deformities (e.g., sphenoid wing dysplasia), three types of neurofibromas and multiple cancers, most commonly neurofibrosarcomas, and on and on and on? Plain and simply, NF1 is likely the disorder to explicate the praxitype and teach us about HOW a phenotype eventuates.

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