MATHEWS Open Access Journals

ISSN: 2572-6536

Commentary Article | Mathews Journal of Neurology

The Praxitype and Phenotype Hierarchies Exemplified by NF1

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Received Date: 01 May 2017

Accepted Date: 19 Jun 2017

Published Date: 21 Jun 2017

Citation: Riccardi VM. (2017). The Praxitype and Phenotype Hierarchies Exemplified by NF1. M J Neur. 2(1): 008.

KEYWORDS

Central Dogma; Genotype; Phenotype; Praxitype; Neurofibromatosis; NF1.

INTRODUCTION

The canonical Central Dogma declared the relationship between a gene (DNA locus), the RNA transcript and the protein product: Gene → mRNA → Protein [1]. This Central Dogma approach was casually adopted to explain genetic disease and, as well, genetic traits in general: Mutant Gene (Allele) → Aberrant mRNA → Abnormal Protein, the latter accounting for the overall phenotype. A popular truncated version of Central Dogma representation used to explain genetic disease over-simplified both the physical dynamics and the underlying logic: Mutant Allele(s) → Mutant Phenotype (γ → ϕ). Knowledge of a mutant gene (allele) foretold the disease phenotype. As simple as that! For many reasons, not the least of which is our recent understanding and characterization of epigenetics and related disciplines, there is much more to pathogenic schemata than change in the nucleotide base sequence in a genetic locus [2-5]. It is not just the mutant gene, but how that mutant gene is physically and chemically manifest, that is, put into *practice* [6]. The word designating this notion of putting a gene into practice is *Praxitype* [7]. The Praxitype consideration is implicit in various relevant phrases, such as "Metabolome" and "Interactome" and so on.

The notion or the various phenomena of "putting a gene into practice" is designated by the term, Praxitype (π), [7] etymologically consistent with the terms Genotype (γ) and Phenotype (ϕ). Thus, the over-simplified formulaic expression γ → ϕ necessarily becomes γ → π → ϕ. In turn, the major efforts in characterizing how a gene (wildtype or mutant) manifests as a trait (normal, variant or pathological) must now focus on the *Praxitype*. Just what are the conditions and factors that account for HOW the gene is realized as a phenotypic trait (element)? For example, what are the general and specific roles of epigenetic silencing, microRNAs, post-translational modification (e.g., phosphorylation), protein sequestration or turnover, etc.? [4, 5, 8] Specifically, the progression, γ → π → ϕ, is not just a matter of the passage of time, it is a matter of the details of various mechanisms employed over time. On the other hand, a disorder's progression over time is often overlooked, for example, that an NF1 neurofibroma is the "same" at all time periods: no, it changes and for at least some changes, the praxitype must be considered.

The *Praxitype* is putting the *Genotype* into practice, [7] the net result of the Praxitype is the *Phenotype*. The latter, the *Phenotype*, almost always contains multiple "elements," the detailed itemization of which declares or describes the *Phenotype*. These elements are related to each other both as members of different classes (hierarchically) and as members of the same class. However, all too often, the individual elements are not sorted out with regard to their respective causal relationships to the *Genotype*. That is, are there hierarchical differences from one phenotypic element to another in the intervening steps between the Genotype and the Phenotype? Is the "practice" more complicated for some elements than for others? Yes, of course! For example, in the autosomal dominant genetic disorder, *Neurofibromatosis* type 1 (NF1), vertebral dysplasia seems to be a *fundamental* element, a Feature causally proximate to the culprit mutation. The associated dystrophic scoliosis element derives from the vertebral dysplasia as a *Consequence*. In turn, the progressive dystrophic scoliosis element can lead to the *Complication* of a spinal cord compression element. Sorting out the *Praxitype* will depend

on and reflect the causal proximity of each element to the ultimate cause, the gene mutation, and, as well, environmental influences.

Unfortunately, *hierarchical relationships of phenotype elements are frequently overlooked or discounted* [7, 9]. This is a mistake: exploration of genetic disease pathogenesis must necessarily identify and respect hierarchical relationships of *Phenotype* elements. The specific hierarchy under consideration here includes Features, Consequences and Complications [7, 10, 11]. The Feature is the phenotypic element most proximate to the influence of the genetic locus itself (i.e., one or both alleles, wildtype, variant or frankly mutant). Cafe-au-Lait Spots, most neurofibromas and vertebral dysplasia phenotype elements are examples of NF1 Features. Atypical neurofibromas (STEP Lesions) and dystrophic scoliosis phenotype elements are examples of NF1 Consequences. Neurofibrosarcoma following on an atypical neurofibroma and spinal cord compression due to dystrophic scoliosis phenotype elements are examples of NF1 Complications.

Trying to account for all three types of NF1 *Phenotype* elements solely on the basis of the NF1 mutant allele(s) seems myopic and narrow-minded. Other, additional aspects of the "genetic machinery" must needs be considered [4]. How the germinal and somatic mutant alleles are "put into practice" ultimately accounts for the hierarchical relationships of the phenotype elements, as well as for the details of each of the Features, Consequences and Complications. Treating each of these three classes of lesions (elements) as though they all had (have) the same pathogenetic causative relation to the alphabetic nature of the mutation is a serious miscalculation.

Throughout the NF1 literature the neurofibroma syndrome is considered to be merely a uniform collection of "features" or "complications," both terms used without the required perspicacity considered above. A frequent and incorrect implicit presumption suggests that all of the syndrome's elements are homogeneous (not hierarchically related) regarding their respective causal relationships to the contributory mutant genes, be they the germinal *NF1* mutation or the patient's myriad distinctive *NF1* somatic mutations. Of course, there also may be some *NF1* allelic interaction or allelic silencing, but, indeed, those details are part of the Praxitype and thus critical to understanding the latter's relevance to understanding NF1 pathogenesis, clinically or for research purposes.

It is often said that an *NF1* mutation itself accounts for one of the disorder's primary features, neurofibromas. But, then, how do we account for the *three different prototypic types* of NF1 neurofibromas? Endoneurial (e.g., cutaneous) neurofibromas are very different from Epineurial (diffuse plexiform) neurofibromas and both of them are very different from Perineurial (subcutaneous and nodular plexiform) neurofibromas [12, 13]. There must be something more to the development of NF1 neurofibromas than the alphabetic details of the mutation itself. Moreover, there are specific and general differences between the NF1 syndrome phenotype when 1) the *NF1* mutation involves an intragenic alteration, in contrast to 2) a whole gene deletion. For these two different types of NF1 distortions, at the least, the allelic interactions would have to be very different, these differences reflecting one particular aspect of *Praxitype* dynamics. In addition, for example, some Epineurial neurofibromas are distinctive for overlying hyperpigmentation and hirsutism, while others – even for a single individual – are free of both overlying hyperpigmentation and hirsutism. This cannot be solely accounted for by the fixed DNA disturbance: there must be additional genetic influences and dynamics at play. Hence, resort to the *Praxitype* and its contributory factors.

Historically, the Central Dogma approach to understanding human genetic disease had a 50-60 year period of immediate utility. It is now time to replace this approach with the Praxitype schema ($\gamma \rightarrow \pi \rightarrow \phi$) and render it to explicate the hierarchy of phenotypic elements (Features → Consequences → Complications) [14-16]. Treatment strategies are likely to be more gene-specific for Features and progressively more general for Consequences and Complications. For example, treatment strategies for dealing with NF1 vertebral dysplasia will be very different from treating one its complications, spinal cord compression.

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