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Short Communication

NF1 and the Praxitype

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Submitted: 19 February 2015

Accepted: 25 June 2015

Published: 27 June 2015

Keywords
- Genotype
- Homology
- Neurofibromatosis Type 1
- NF1
- Phenotype
- Praxitype
- Supergene

Abstract

The human genetic disorder, Neurofibromatosis Type 1 (NF1), by virtue of its well-studied variability and complexity, presents a compelling opportunity to examine the relationships of genotypes and phenotypes in general. A new concept, the *praxitype*, is introduced as a means of designating and accounting for the complex biochemical and genetic interactions interposed between the canonical genotype and phenotype.

ABBREVIATIONS

CT: Contagion; ED: Epidemic Disease; IA: Infectious Agent; γ: Genotype; φ: Phenotype; π: Praxitype

INTRODUCTION

Classical genetics at all levels through to modern medical genetics has relied on two phrases to deal with the relationship of the heritable element – DNA – to its biochemical, cellular, tissue, organ and organismal consequences. These two phrases are *genotype* and *phenotype* and they have been used as though the relationship between them is obvious and singular. I would posit that this simplification, usually implicitly ignored or skirted, now needs to be investigated carefully and, as an element thereof, displaced by a concept and phrase commensurate with the etymology and utility of the original two phrases/concepts, namely genotype and phenotype [1]. To this end, I propose the term, praxitype, a word that literally allows for and designates the practice or mechanism by which phenotype elements derive from genotypes. In short, *praxitype* goes beyond allowing to absolutely requiring a specific combination of mechanisms or modalities by which the phenotype derives from the genotype [2].

How the DNA code is rendered as a specific phenotype we know to be extraordinarily complex for at least selected gene loci, not the least of which is *NF1* [3-6].Yesteryear's "Central Dogma" schema (DNA → RNA → Protein) has served its purpose and it is now time to consider more exactly the multiple schemata that contribute to translating chromosomally-organized DNA to biochemical, cellular, tissue, organ and organismal phenotypes. [2;7] It is not my intention either to itemize or to characterize each of the schemata. Rather, I wish to establish that there is indeed a category of such phenomena, the recognition of which will facilitate – even foment – establishment of a hierarchy of these phenomena. That category is the *praxitype*. At the outset, I expect that each genetic locus will have a prototypic praxitype, with alternative, subordinate praxitypes employed as a function of factors yet to be determined.

As a noun, the word, *practice*, is commonly defined as "the actual application or use of an idea, belief or method, as opposed to the theories about such application or use." (Google Online, 23 September 2014) Alternatively, as a verb, practice is defined as the ability to "carry out or perform a particular activity, method or custom habitually or regularly." (Google Online, 23 September 2014) Ultimately, these definitions derive etymologically from the Greek verb "prasso" (πρασσω), "to achieve, bring about, effect, accomplish." (Wikipedia, 23 September 2014) From a genetic vantage point, the *genotype* (γ) literally encodes certain details about what is to be accomplished, the latter traditionally referred to as the phenotype (φ). What has been left out is the sum of practices (or practices as this verb is spelled in British parlance) that translate or transform the γ code variously into one or more φ. The key is that there are multiple (types of) practices that influence the transformation, for example, transcriptional editing, post-translational modifications, imprinting, the influences of miRNA and lncRNA, and the direct and indirect interactions with other gene loci and their peptide/protein products. Again, the sum of these practices, that is, the *praxitype* (π), is more or less distinctive for each locus, such that the full spectrum of a φ depends as much on the π of the locus as on its γ. The *NF1* gene locus demonstrates this principle exquisitely, [8;9] especially when its γ has been altered (mutated or deleted) [8-12]. A mutated *NF1* γ restricts and/or expands the π distinctively for each mutation's φ. Being able to itemize the elements of both the π typical of the wildtype γ and the π typical of various classes of mutant *NF1* γ is likely critical for understanding the molecular pathogenesis of the NF1 syndrome in terms of it multiple features, consequences and complications [13].

Very large genes with multiple domains are likely to have a comparably complex praxitype (or set of praxitypes). The *NF1* gene almost certainly is representative of this consideration.[14] More generally, perhaps the notion of "supergenes" will be more amenable to explication through the application of the praxitype

concept [15]. Supergenes were originally considered to account for mimicry [16] and homology, [14;17-19] but more recently for ordinary developmental phenomena[7;20] and cancer [2]. In these regards, a brief consideration of homology and related issues may be helpful in elucidating praxitypes.

Homology, Analogy and Identity

The *Online Merriam Webster Dictionary* (as of 20 July 2014) provides a starting place for considering cross-species comparisons, with particular regard to the related notions of homology and analogy. This source's first three considerations of *homology* include the following. "1) a similarity often attributable to common origin; 2) a. likeness in structure between parts of different organisms (as the wing of a bat and the human arm) due to evolutionary differentiation from a corresponding part in a common ancestor; b. correspondence in structure between a series of parts (as vertebrae) in the same individual; 3) similarity of nucleotide or amino acid sequence (as in nucleic acids or proteins)." The four considerations of *analogy* were the following. "1) the inference that, if two or more things agree with one another in some respects, they will probably agree in others; 2) a. the resemblance in some particulars between things otherwise unlike; b. the comparison based on such resemblance; 3) the correspondence between the members of pairs or sets of linguistic forms that serves as a basis for the creation of another form; 4) the correspondence in function between anatomical parts of different structure and origin."

Our current approaches to understanding NF1 syndromes in general and NF1 neurofibromas specifically derives in large part from multiple, sometimes distantly related species. The most frequently used non-human metazoan organisms include *Drosophila melanogaster*, [21-30] *Fugu rubripes*, [31-33] zebrafish (*Danio rerio*),[34-38] Bicolor damselfish, [39-59] *Mus musculus*, [60-83]. Several species of the genus, *Rattus*, [84-91] *Bos primigenius taurus* (Holstein cattle, etc.) [92-100] and chickens [101-105]. Given this heterogeneity of insects, teleosts, bovines, fowl and murines, we should be especially mindful as to whether the anatomic structures (and mutation-based lesions) are related to each other as "identical," homologies or analogies [106-108]. For example, the wings of *Drosophila* and of bats are analogous, while the limbs of mice and humans are homologous. What about the nerves and ganglia of Drosophila? Are they "identical" to those of humans; or homologous or analogous? The lack of Schwann cells in *Drosophila* nerves, as well as these nerves' distinctive patterns of formation, suggests that *Drosophila* and human nerves are more likely analogous than homologous. On the one hand, there is the lack of neurofibromas in *D. melanogaster nf1* mutants [30,109]. On the other hand, a nerve overgrowth lesion "similar" to that seen in human NF1 is a result of *egghead* mutations (*egh*-/-) [30,109]. These two facts are critically relevant to elucidation of the praxitype. The overlap of the species-specific mutant phenotypes is more likely explained by the similarity of praxitypes than by the similarity of genotypes. In any event, this approach to comparative pathogenesis [106,108,110] has not heretofore been appropriately taken into account in exploring the origins and treatment strategies for the human NF1 syndrome and its individual lesions.

Genes/DNA and proteins on the one hand, and anatomic structures, including cell types, such as mast cells [111] and Schwann cells, [30,112-114] on the other hand, are often different from one species to another. Excessively casual use of the notion of homology in comparing the male prostate to the female counterpart, the urethrovaginal glands [115-125] represents another concrete example of the need for more perspicacity in such comparisons. Moreover, comparing multifaceted homologous structures leads to consideration of a unique type of gene, the supergene, [17-19,114,126] which type I propose is especially relevant to the *NF1* locus. That is, complex phenotypes, whether wildtype or mutant, are more likely to involve complex genetic organization, either on the basis of syntenic gene clusters resistant to recombination [18,19,127-130] or supergene Mendelian loci *sensu strictu* [19;131-133]. Again, a key consequence of this treatise is the utilitarian proposal that the very large and complex *NF1* gene is a supergene critical to the evolution of *Homo sapiens* in terms of the species' distinctive, definitive elements. Intrinsic to these considerations is the need to focus *both* on the function of *NF1* wildtype alleles (especially in terms of praxitypes and phenotypes) and on a more perspicacious sorting out of the NF1 syndrome phenotypes in terms of distinguishing its elements as either features, consequences or complications [13].

This homology interlude especially emphasizes the need to be more expansive – and simultaneously more precise – in our characterization of phenotypes: both for inter-species comparisons and for acknowledging that the DNA alphabetic sequence is only part of the genetic story. We also need to know the details of how the DNA yields the phenotypes being compared. While the DNA sequences account for the similarities, it is the praxitypes that account for the differences.

The Praxitype and Contagion

Above, I proposed a model of the paired *genotype* (γ) and *phenotype* (φ), which, for completeness, requires the *praxitype* (π). For further clarification, I suggest a comparison with the established canonical model of the paired *infectious agent*, or IA (virus, microbe, parasite), and associated epidemic disease, or ED (clinical syndrome), combined with the epidemiological control element, *contagion* (CT). Modalities relevant to the practices and control of contagion include administrative actions such as swamp drainage, DDT spraying and so on. These administrative actions are directed at the contagion parameters, not simply at the culprit organism. The focus is on the operational elements – the "practices" – of selected IA populations [134]. In order to control – to some realistic degree – infectious diseases characterized, if not defined, by human epidemics, solely detailing individual organisms (e.g., *Vibrio cholera*) does not afford a way to control the epidemics. Rather, it is the details about how a population of IAs interact with – engage in a practice with – populations of humans (and usually other organisms as well). Parenthetically, understanding "swarming" typical of certain organisms is not decipherable from even the most detailed analysis of an individual organism within a species. The behavior of the population of individuals during the swarming activity must be the target for investigation and elucidation of swarming [135-137].

For genetic disorders or, more generally, their phenotypes, as with epidemic infectious diseases (plagues), one must go beyond the individual organisms (or, sometimes, simply their different

cell types) to consideration of public health principles and such. Understanding genetics and overcoming genetic disease is impossible without recognizing and influencing the praxitype, the phenomena or practices connecting genotype with phenotype, γ with φ. I suggest that the notion of contagion is comparable to the notion of praxitype in understanding critical elements of the relationship of genotype to phenotype. We have gone from (IA → ED) to (IA → CT → ED) for epidemic infectious diseases and now must go from (γ → φ) to (γ → π → φ) for genetics and genetic disorders.

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Cite this article

Riccardi VM (2015) NF1 and the Praxitype. JSM Genet Genomics 2(1): 1006.