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Editorial

Multiplicity as a Factor in Understanding NF1

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The NF1 locus on the long arm of chromosome 17 is a very special gene in the human genome. In terms of *multiplicity*, there are five pseudogenes on five other chromosomes; it influences the formation and/or behavior of many tissues; it is probably the locus with highest germinal mutation rate in humans (1 in 10,000), with a disease frequency of 1/2,500-1/3,000. There are several other *multiplicities* that persist in confounding our understanding of this very common autosomal dominant disorder. This editorial focuses on three considerations: 1) How many types of Neurofibromatosis (NF) are there? 2) How many types of NF1 neurofibromas are there? 3) What are the logical/causative relationships of the numerous pathogenetic and clinical elements of the full-blown syndrome or portions of it?

TYPES OF NEUROFIBROMATOSIS (NF)

In 1982[1] and for the first two editions of my NF book.[2,3] I identified seven to eight relatively distinctive types of NF. Based on careful literature reviews, the most common and most consistent phenotype was labeled as NF1. The next most consistent and somewhat common phenotype, with bilateral vestibular schwannomas as the hallmark, was labeled NF2. The remainder of NF "types" were characterized as to the presence and/or distribution of neurofibromas, time of onset, idiosyncratic elements, and such. They were sequentially labeled NF3 through NF7 and NF-NOS (Not Otherwise Specified). Schwannomatosis, as a distinct entity was not considered in the earliest characterizations. In 1987, an NIH Consensus Conference adopted the NF1 and NF2 terminology as alternatives to "Von Recklinghausen disease (VRD)" and "Bilateral Vestibular Schwannomas," respectively.[4] The respective gene loci have long been established on 17q11.2 and 22q12.2.[5,6]

The point is that the numerical basis for NF classification and nomenclature reflects was pre-genomic clinical heterogeneity, most useful in characterizing subtypes of what was originally called Von Recklinghausen Disease. The only exceptions were the two non-neurofibroma disorders: NF2 is a totally distinct schwannoma-generating disorder, as is Schwannomatosis; and NF5 identified what we now know as the Legius syndrome. An important general point here is that a body-wide distribution of multiple neurofibromas is virtually always a type of VRD or NF1. In addition, an intragenic mutation or a whole gene deletion (WGD) involving the NF1 locus consistently manifests as some iteration of the VRD phenotype.[7,8]

In other words, etiologically, there appears to be only one disorder that accurately warrants the diagnosis sensu strictu (phenotype attribution) of Neurofibromatosis or NF. For the time being, it would reserve the diagnostic or phenotypic label of Neurofibromatosis 1 or NF1 for an intragenic mutation or WGD involving the NF1 locus at 17q11.2.

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TYPES OF NEUROFIBROMAS

AThe key to VRD or NF1 is the neurofibroma. And there is more than one type of neurofibroma, although sadly there is not yet consensus for their logical classification or names. Respecting that all neurofibromas are accurately and consistently considered to be Peripheral Nerve Sheath Tumors (PNSTs), in 2007.[9] It was proposed that there are three basic types of neurofibromas consistent with all prior classifications and routine histopathological designations: *Endoneurial*, *Epineurial* and *Perineurial*. Their similarities and differences are emphasized in Table 1. Key elements for the

Plexiform nf (Pnf) are 1) the absence/presence of a Central Nervous System (CNS) connection, likely associated with the neurofibrosarcoma risk; and 2) recognition of two types of Pnf. It has elaborated on these similarities and differences on multiple occasions.[10,11]

Table 1. NF1 Neurofibroma Types

Endoneurial (Pierre Masson "Diffuse;"[12] No CNS Connection)
Endoneurium Only
No Intact Perineurium
No Intact Epineurium
Cnf; NMJnf; CRUSHnf
Epineurial (Pierre Masson "Diffuse;" + CNS Connection)
Endoneurium Present
No Intact Perineurium
Initial Intact Epineurium
Diffuse Pnf
Perineurial (Pierre Masson "Encapsulated;"[12] + CNS Connection)
Endoneurium Present
Intact Perineurium
Intact Epineurium
Subcutaneous nf; Nodular Pnf

NF1 PATHOGENETIC AND CLINICAL ELEMENTS

VRD or NF1 is characterized, if not defined by neurofibromas, but universally there are multiple additional pathophysiological and clinical elements that are not respected as to how immediate is the genetic change (mutant genotype) to the clinical consequence (mutant phenotype): they are all simply (and often erroneously) referred to as "features" or "complications" of the disorder. This over-simplification severely retards understanding the disorder's pathogenesis. HOW the mutant genotype is literally put into practice to account for the phenotype – that is, the mutant genotype's *Praxitype* – is the key to understanding NF1's pathogenesis, especially as regards treatment approaches.[10,13,14] For example, the NF1 element usually referred to as *Vertebral Dysplasia* is a (primary level) feature of the disorder, while the oft-resulting *Dystrophic Scoliosis* is one (secondary level) consequence of the feature. In turn, a resulting *Spinal Cord Compression* may be a (tertiary level) complication of the consequence. Distinguishing the multiple types of pathogenetic elements of NF1 is key to understanding and treating this complex, complicated disorder. As with realizing whether there are multiple types of NF1 and distinguishing the multiple types of NF1 neurofibromas, realizing that there are multiple levels, multiple types of pathogenetic and clinical elements is one of the keys to understanding and, eventually, effectively treating this challenging genetic disease.

REFERENCES

1. Riccardi VM. The multiple forms of neurofibromatosis. *Pediatr Rev.* 1982; 3: 292-298.

2. Riccardi VM, Eichner JE. *Neurofibromatosis: Phenotype, Natural History, and Pathogenesis*. Baltimore, USA: Johns Hopkins University Press; 1986.

3. Riccardi VM. *Neurofibromatosis: Phenotype, Natural History and Pathogenesis*. Baltimore, USA: Johns Hopkins University Press; 1992.

4. Neurofibromatosis. Conference statement. National institutes of health consensus development conference. *Arch Neurol.* 1988; 45: 575-578.

5. Ledbetter DH, Rich DC, O'Conell P, et al. Precise localization of NF-1 to 17q11.2 by balanced translocation. *Am J Hum Genet.* 1989; 44: 20-24.

6. Arai E, Ikeuchi T, Nakamura Y. Characterization of the translocation breakpoint on chromosome 22q12.2 in a patient with neurofibromatosis type 2 (NF2). *Hum Molec Genet.* 1994; 3: 937-938.

7. Kluwe L, Siebert R, Gesk S, et al. Screening 500 unselected neurofibromatosis 1 patients for deletions of the Nf1 gene. *Hum Mutat.* 2004; 23: 111-116. doi: 10.1002/humu.10299

8. Upadhyaya M, Kluwe L, Spurlock G, et al. Germline and somatic NF1 gene mutation spectrum in NF1-associated malignant peripheral nerve sheath tumors (MPNSTs). *Hum Mutat.* 2008; 29: 74-82. doi: 10.1002/humu.20601

9. Riccardi VM. The genetic predisposition to and histogenesis of neurofibromas and neurofibrosarcoma in neurofibromatosis type 1. *Neurosurg Focus.* 2007; 22(6): 1-11.

10. Riccardi VM. Translational genetics and genomics: The fundamental nature of NF1 neurofibromas. *J Transl Genet Genom.* 2017; 1: 1-12.

11. Riccardi VM. NF1 clinical elements and the NF1 neurofibroma Burden. *Jacobs J Neurol Neurosci.* 2016; 3(1): 025.

12. Masson P. *Human tumors: Histology, Diagnosis, Technique*. Detroit, USA: Wayne State University Press; 1970.

13. Riccardi VM. NF1 and the Praxitype. *JSM Genet Genomics.* 2015; 2: 1006.

14. Riccardi VM. The Praxitype and Phenotype Hierarchies Exemplified by NF1. *Mathews J Neurol.* 2017; 2: 1-3.