Journal of Genetics and Cell Biology
JGCB, 3(3): 205-206
www.scitcentral.com

ISSN: 2639-3360

Original Research Article: Open Access

Permission for Nf1 Somatic Mutation

Vincent M Riccardi*

*The Neurofibromatosis Institute, Canada.

Received April 20, 2020; Revised May 08, 2020; Accepted May 10, 2020

ABSTRACT

In the progression of the disorder, Neurofibromatosis 1, NF1 Somatic Mutation (SM) is extraordinarily important. In this context it makes sense to query how NF1 SMs eventuate in this disorder. For example, what part of the cell cycle contributes to NF1 SM? In general, the SM process requires DNA synthesis, in turn a sine qua non of cell division, of cell proliferation. Thus, presumably, details of cell proliferation determine when and where an intragenic mutation occurs (although an intragenic deletion or whole gene deletion might occur at other times in the cell's history). In either case, does this have anything to do with the very large size of the NF1 locus and the very large size of the NF1gene product, Neurofibromin (Nfn)? Importantly, the duration of NF1 DNA replication or synthesis (S-phase) overlaps with the duration of DNA translation to messenger RNA (G_1-phase or G_2-phase), such that there could be compromise of the DNA synthesis so as to corrupt the latter's completion. Multiple studies have documented that an NF1 person's cutaneous neurofibromas (Cnfs)each have a distinct NF1SM, even if the Cnfs are spatially close to one another [1]. That is, it would seem that the basis for and the nature of the mechanism accounting for each NF1 SM is intrinsic to the cell, and not to some paracrine, endocrine or other extracellular factor(s).

INTRODUCTION

Cnfs are rarely, if ever, present in NF1 newborns, although a diffuse plexiform neurofibroma (Pnf) may present in the newborn period or early childhood. However, beginning just before or during puberty, Cnfs begin developing, with accelerating numbers over time. Even when Cnfs number in the hundreds, or even thousands, each Cnf is associated with a unique (i.e., de novo) SM. If a single mechanism or a single factor associated with cell proliferation accounted for all instances of SM, we would anticipate that a zygote bearing a germinalNF1 mutation or deletion would give rise to huge numbers of embryonic, fetal and newborn cells with anNF1 SM – in neurofibromas and otherwise. Actually, contrary to this potential outcome, the vast majority of NF1 newborns seem to be ostensibly normal. What is it about embryologic and fetal development that accounts for the difference compared to later childhood and adult life? Or is it something(s) about childhood and adult life?

Either the NF1 SM phenomenon is suppressed in utero and/or it is accelerated subsequently. I have posited previously [2,3] that an NF1 Cnf can be initiated by local mild-to-modest trauma. This trauma, or a related phenomenon, leads to the earliest stage of Cnf (i.e., the Pre-Cnf [4] or the Cnf nascent/latent phase [5,6]), which then proceeds to the stage characterized by NF1 SM and then maturation into a later stage overt Cnf. As Endoneurial neurofibromas [7], Cnf are pathophysiologically distinct from the other types of NF1 neurofibromas. While diffuse Pnfs (i.e., Epineurial neurofibromas [7]) are basically congenital lesions, perineurium-intact Nodular Pnfs and Subcutaneous neurofibromas (i.e. Perineuria neurofibromas) occur in childhood and adulthood.

The human fetus is said to be the product of 41 doublings, starting with the zygote. At 5 doublings there are 64 cells. At 20 doublings there are 2,097,152 (2.10×10^6) cells. At 40 doublings there are 1.65 trillion (1.65×10^{12}) cells. At 45 doublings there would be 53 trillion (5.27×10^{13}) cells. The point is that there are billions and trillions of cells experiencing cell divisions and DNA synthesis over the nine-month gestational period. Given the very high rate of NF1 SM in adult NF1 Cnfs, this virtual absence in the embryo and fetus is remarkable, if not startling. Does something "suppress" NF1SM in utero or does something "accelerate" NF1SM subsequently? In either case, refining these observations seems cogent.

Corresponding author: Vincent M Riccardi, MD, MBA Director, The Neurofibromatosis Institute, 5415 Briggs Avenue La Crescenta, CA, Tel: 91214818-93508; E-mail: riccardi@medconsumer.com

Citation: Riccardi VM. (2020) Permission for Nf1 Somatic Mutation. J Genet Cell Biol, 3(3): 205-206.

Is it a matter of a distinct strategic genetic locus that influences thisNF1 SM process? Or is it a matter of ordinary multifaceted genetic loci being subjected to disturbed epigenetic influences? Is it a matter of what the gene is, as opposed to how the (mutant) gene is "put into action?" In short, is it a matter of the built-in information at the NF1 genetic locus or the Praxitype? [8-10]. (The Praxitype accounts for how a gene are put into practice, in contrast to the genotype, what the genetic locus literally encodes in its DNA.) Respecting that the initiation and/or progression of NF1 clinical elements is ordinarily associated with NF1 SM, it is surprising – if not peculiar – that almost no intense investigation on the origins of NF1 SM has been carried out [11] or even promoted! Perhaps the present discussion will contribute to a change in this regard and foster investigation into the pathogenetic mechanism(s) underlying NF1 SM.

REFERENCES

1. Guengerich FP (2008) Cytochrome p450 and chemical toxicology. Chem Res Toxicol 21: 70-83.
2. Thomas L, Kluwe L, Chuzhanova N, Mautner V, Upadhyaya M, et al. (2010) Analysis of NF1 somatic mutations in cutaneous neurofibromas from patients with high tumor burden. Neurogenetics.
3. Riccardi VM (1992) Neurofibromatosis: Phenotype, Natural History and Pathogenesis. Baltimore: Johns Hopkins University Press.
4. Riccardi VM (2016) NF1 Clinical Elements and the NF1 Neurofibroma Burden. Jacobs J Neurol Neurosci 3: 0-25.
5. Rice FL, Houk G, Wymer JP (2019) The evolution and multi-molecular properties of NF1 cutaneous neurofibromas originating from C-fiber sensory endings and terminal Schwann cells at normal sites of sensory terminations in the skin. PLos One 14: e0216527.
6. Riccardi VM (2017) Translational genetics and genomics: The fundamental nature of NF1 Neurofibromas. J Transl Genet Genom 1: 1-12
7. Ortonne N, Wolkenstein P, Blakeley JO (2018) Cutaneous neurofibromas: Current clinical and pathologic issues. Neurology 91: S5-S13
8. Riccardi VM (2007) The genetic predisposition to and histogenesis of neurofibromas and neurofibrosarcoma in neurofibromatosis type 1. Neurosurg Focus 22E3: 1-11
9. Riccardi VM (2017) The praxitype and phenotype hierarchies exemplified by NF1. Mathews J Neurol 2: 1-3
10. Riccardi VM (2018) The praxitype and genetic arithmetic. J Transl Sci 4: 1
11. Riccardi VM (2019) The praxitype: An improved interpretation of genotype-phenotype variation. Neuro Open J 6: 10-12.
12. Allaway RJ, Gosline SJC, La Rosa S (2018) Cutaneous neurofibromas in the genomics era: Current understanding and open questions. Br J Cancer 118: 1539-1548.