

Permission for Nf1 Somatic Mutation

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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 NF1 gene product, Neurofibromin (Nfn)? Importantly, the duration of NF1 DNA replication or synthesis (S-phase) overlaps with the duration of DNA translation to messenger RNA (G₁-phase or G₂-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 NF1 SM, 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 germinal NF1 mutation or deletion would give rise to huge numbers of embryonic, fetal and newborn cells with an NF1 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. Perineurial 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" NF1 SM in utero or does something "accelerate" NF1 SM subsequently? In either case, refining these observations seems cogent.

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Is it a matter of a distinct strategic genetic locus that influences this NF1 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.

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