

Editorial

To stop the progression of *neurofibromatosis 1*, a somatic mutation causes cellular apoptosis

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Article information

Accepted: July 4th, 2025; Published: July 12th, 2025

Cite this article

Riccardi VM. To stop the progression of neurofibromatosis 1, a somatic mutation causes cellular apoptosis. *Neuro Open J.* 2025; 11(1): e1-e2.

Persons with ordinary, prototypical *Neurofibromatosis 1* (*NF1*) are born with a germinal/zygotic mutation at the *NF1* locus on the long arm of chromosome 17 (17q) present in all of their cells. An *NF1* germinal mutation is the “first hit,” accounting for haploinsufficiency at the *NF1* locus. The *NF1* somatic mutation is the “second hit,” accounting for diploinsufficiency (deranged or lost function of both alleles) at the *NF1* locus. The *NF1* somatic mutation occurs in a variety of somatic (i.e., non-germinal) cells, including, and especially the schwann cells (SC). I suggest that *NF1* haploinsufficiency provides the conditions for the SC (and other cells) to develop *NF1* diploinsufficiency rather than *NF1* diploinsufficiency developing independently of the conditions in which it originates. In either case, imagine a viral analogue with an apoptosis trigger held in abeyance unless an *NF1* somatic mutation occurs in the presence of an *NF1* germinal mutation or whole gene deletion. That is, instead of altering the feature, for example, decreasing neurofibroma size and symptoms with MEK inhibitors, I herein suggest an approach to preventing certain *NF1* features, keying off the fact that almost *NF1* features involve somatic mutation of the cell’s *NF1* wild type (WT) allele.

The *NF1* phenotype, that is, the *NF1* syndrome, has many elements, not all with the same “causal relationship” to *NF1* genotype. *NF1* features are elements closest in causal proximity to the genomic disturbance, for example, neurofibromas or vertebral dysplasia.¹ *NF1* consequences, derived from *NF1* features, include atypical neurofibromas and spinal scoliosis.¹ *NF1* complications, derived from *NF1* consequences, include neurofibrosarcoma and spinal cord compression.¹ Respecting the publication of E.L. Rice and colleagues,² there is also the matter of the precursor of the *NF1* feature. Their article emphasizes the importance of *NF1* syndrome elements that are precursors to the syndrome’s characteristic features. Specifically, they describe a precursor to the *NF1* cutaneous neurofibroma (cNF). One important question the

article raises is the presence or timing of the *NF1* somatic mutation with regard to the development of the *NF1* feature. Does the *NF1* somatic mutation derive the precursor or does the *NF1* somatic mutation account for the conversion of the precursor to the feature? I expect that often it is the latter. Respecting this general type of reasoning, perhaps the *NF1* syndrome progression could be reversed or stopped early on through genetic manipulation before elements of the disorder compromised the person. For example, we could modify the zygote’s *NF1* mutation, amplify expression of wildtype allele or use the occurrence of an *NF1* somatic mutation as a trigger to remove the affected cell through induced apoptosis.

Many factors other than the *NF1* locus or the latter’s protein product, Neurofibromin (Nfn), might or can influence Cnf development, such as mast cells,³ collagen deposition⁴ and skin adnexae.⁵ Rice, et al² makes a clear case for cell-cell cooperativity in *NF1* syndrome skin potentially contributing to the development of *NF1* diploinsufficiency. Terminal sensory axons in the skin are not always associated with other skin components (sweat glands, sebaceous glands, sweat ducts, vascular bundles, etc.). But, when they are, SCs may be dislodged from the involved nerve and proliferate according to new schedules. Such cell divisions afford new opportunities for the occurrence of SC *NF1* somatic mutations, ultimately affording both *NF1* haploinsufficient SC and *NF1* diploinsufficient SC accumulations, in turn providing a cellular and intercellular conglomeration that either anticipates or represents an early-stage cNF. The overall point is that something about *NF1* haploinsufficient cellular cooperativity affords the opportunity for, or actually triggers, *NF1* somatic mutations.^{6,7}

As one peruses the natural history of the *NF1* syndrome at the cellular level, recurrent *NF1* diploinsufficiency, that is, recurrent *NF1* somatic mutation, occurs very frequently

in multiple types of tissue, including that of the central nervous system, the peripheral nervous system, the skin, the skeleton, stem cells, endocrine glands, the vascular system, the pulmonary parenchyma, etc. In a seventh-decade *NF1* adult, thousands of somatic mutations may have occurred. Exactly why this happens has escaped clarification, but these somatic mutations can be usurped or obviated nonetheless, as suggested herein.

Recently, a significant portion of medical genetics clinical research has shifted from focusing on a disorder's natural history to genetic modification, which, for example, might convert a genetic mutation "back" to the normal (i.e., wildtype allele). Respecting this general type of reasoning, it seems that the *NF1* syndrome features (*sensu strictu*) could be prevented early on through genetic manipulation. Gene editing has garnered the most interest, using deoxyribonucleic acid (DNA)-editing substances such as CRISPR/Cas9.⁸ The restorative molecule is introduced into each of the organism's cell nuclei, the DNA region of interest identified and that region modified from the mutant structure to a wildtype allele.^{9,10} However, although CRISPR/Cas9 cell-by-cell gene editing has substantial potential benefits, it is fraught with technical, political and ethical problems.

Increasing WT *NF1* gene expression, especially cogent when the initial (germinal or zygotic) genetic change involves a whole gene deletion, involves increasing the WT allele's protein production to more than is usual or ordinary for the WT allele. However, one wonders about increasing the "activity" of Nfn in all cells, since the *NF1* gene locus might normally be silent or quiescent in certain cell types. In cells in which it is not ordinary, *NF1* gene expression might have serious negative repercussions. For the *NF1* gene (locus), it is not clear that both alleles are equally expressed. Nor is it clear whether the monoallelic protein product functions on its own as a monomer or pairs as a dimer; and, if it is a dimer, whether the two parts derive from the same or different alleles.

Immediate removal of *NF1* diploinsufficient cells is probably the safest genetic treatment approach for interfering with progression of the disorder by imposing a penalty for a particular development within the cell. What I have in mind here is a molecule constructed like, and emulating, a virus homologue or paralogue. This molecular construct would occupy the nucleus in each of the *NF1* person's cells and has two critical abilities: 1) monitoring the long arm of Chromosome 17 to sense that the *NF1* wildtype allele is present; 2) triggering initiation of apoptosis in the event of loss of the *NF1* wildtype allele. In this way, any cell that converts from *NF1* haploinsufficiency to *NF1* diploinsufficiency will be shed immediately from the person through apoptosis. If the *NF1* wildtype allele realizes an intragenic mutation or whole gene deletion, the monitoring system activates cell-specific apoptosis. None of the *NF1* person's cells would be able to survive the

change from *NF1* haploinsufficiency to *NF1* diploinsufficiency.

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