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Biome depletion in conjunction with evolutionary mismatches could play a role in the etiology of neurofibromatosis 1

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ABSTRACT

Neurofibromatosis 1 (NF1) arises *de novo* in a striking 30–50% of cases, pointing toward an environmental etiology, though none has been clearly identified. The Biome Depletion Theory posits that the absence of mutualistic and commensal organisms within the human body coupled with modern lifestyle alterations may have profoundly deleterious effects, inclusive of immunologic derangement that is thought to result in allergy, atopy, and numerous autoimmune diseases. Biome depletion has been implicated as a factor in the etiology of both multiple sclerosis and autism spectrum disorders; biome reconstitution, i.e. replenishment of the biome with certain keynote species, is being used in the treatment of these and other autoimmune states. Neurofibromatosis 1 has been associated with allergy, various autoimmune states, multiple sclerosis, and autism. Recent research has posited that NF1, multiple sclerosis and autism may all arise from disturbances in the neural crest during gestation. This paper hypothesizes that there is indirect evidence that a highly inflammatory uterine state may precipitate epigenetic changes in vulnerable NF-related genes in the course of fetal development. The etiology of NF1 may lie in the absence of immunomodulation by commensal and mutualistic species once ubiquitously present in the environment, as well as through adoption of a modern lifestyle that contributes to chronic inflammation. Replenishment of helminths and other missing organisms to the human biome prior to conception as well as addressing nutritional status, psychological stress, and environmental exposures may prevent the development of NF1. ©Donna L. Beales.

Hypothesis

The hypothesis under consideration in this paper is as follows: (1) fundamental shifts in the modern environment including the absence of symbiotic organisms from the human inner ecology (biome), particularly helminths, may create an abnormally inflammatory and immunologically hyper-reactive *in utero* environment; (2) in genetically predisposed individuals, during pregnancy, when any number of noxious "triggers" manifest within the organism-depleted hyper-responsive uterine environment, inclusive of factors such as hypovitaminosis D, a high degree of unrelenting psychological stress, exposure to environmental toxins, infections, or combinations thereof, these triggers may epigenetically affect vulnerable genes related to the development of Neurofibromatosis and precipitate *de novo* occurrences of neurofibromatosis 1 (NF1); (3) by prophylactically restoring organisms, particularly helminths, to the biome of healthy individuals who carry NF-related genes, and prenatally addressing correctable issues such as vitamin D deficiency, psychological stress, and exposure to environmental triggers, it is theoretically possible that the occurrence of *de novo* NF1 mutations might be prevented.

Introduction

Neurofibromatosis 1 (NF1) is a disfiguring autosomal dominant condition with an incidence of 1/3000–4000, making it one of the most common genetic abnormalities in the population [1,2]. NF1 appears to have no ethnic predilection and manifests in a seemingly uniform geographic distribution, although data used to model geographical patterning of the disease is now considered outmoded, and there is some evidence to support that prevalence may differ globally [3–8].

The condition has a widely variable presentation, and it can result in significant morbidity and mortality. It is typically characterized by the presence of axillary and inguinal freckling, Lisch nodules, optic gliomas, numerous café-au-lait macules and the development of neurofibromas and plexiform neuromas. Diagnosis is based on accepted NIH criteria [9], but genetic testing is also available [2].

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NF1 appears to arise from mutations in the *neurofibromin 1* gene [10]. It is considered a "rasopathy," and has associations with various other RAS signaling disorders [11], speculatively inclusive of autism [12]. NF1 is passed predictably in an autosomal dominant inheritance pattern with complete penetrance, however, strikingly, an estimated 30–50% of newly diagnosed cases appear to arise *de novo* [2,13,17].

NF1 can sometimes present in mosaic form [14]. At least one variety of NF1 has been discovered to exist with an atypical cutaneous presentation and the absence of neurofibromas, a finding which may account for some cases arising seemingly without familial precedent. However, such cases are unlikely to account for the entirety of *de novo* mutations [15,16].

There is strong interest in what precipitates *neurofibromin 1* gene mutations. While genotype unequivocally plays a role in NF1 disease development, the "unusually high" number of spontaneously occurring cases seems to point toward an environmental etiology [6,17].

It is known, for example, that in a rat model, gestational CNS exposure to ethylnitrosourea, a strong mutagen factor in rodents, precipitates neurofibroma formation [18]. Therefore, it seems logical to consider a variety of external environmental insults as potential contributors to disease origin.

To date, multiple singular environmental factors such as parental age [19], folic acid intake [20] and smoking [21] have been implicated, although none has yet been specifically identified that would fully account for the high *de novo* percentage. These findings are the subject of current debate in NF1 research.

NF1, allergy and autoimmunity—a correlation

NF1 has been associated with mast cell disturbances common to allergic and autoimmune disease states, and involving host-bacterial immunity [22–24]. Related to known mast cell physiology, IgE levels are elevated in NF1 patients with plexiform neuromas (PNs), a finding seemingly correlating with PN size [25].

Rasopathies appear to have an association with autoimmune diseases [26]. A correlation between NF1 and various autoimmune conditions has been observed, but the association is considered controversial.

The following Pubmed search was conducted to determine an approximate number of published reports or other studies of autoimmunity in NF1. Some, but not all, common autoimmune states were included, selected because these disease states have been specifically targeted for study using therapeutic helminths, the reason for which will be further elucidated below:

(((neurofibromatosis) AND (autoimm*))
OR ((neurofibromatosis) AND (immunology))
OR ((neurofibromatosis) AND (allerg*))))
OR (((lupus OR multiple sclerosis OR sjogren*
OR ulcerative colitis OR crohn's OR rheumatoid arthritis
OR psoriasis OR autism OR diabetes)) AND neurofibromatos*)

Results revealed that exclusive of autism, which will be discussed separately, 45 papers and/or reports existed at time of search. Multiple sclerosis (MS) appears to be the most often cited NF1-associated autoimmune disease state, followed by psoriasis, lupus, diabetes subtypes, autoimmune hemolysis, thyroiditis, and ulcerative colitis. The actual number of patients reported with these conditions is unknown. The oldest reported finding dates from 1963 (Table 1).

Clearly, there has been notable attention paid in the literature to a correlation between some common autoimmune diseases and NF1. Given NF1's association with mast cell disturbance, which will be discussed in some detail below, this finding is perhaps not surprising. However, more studies are needed to definitively settle the question of the role of autoimmunity in NF1.

Table 1
Number of studies in Medline relating NF1 to various autoimmune conditions.

Condition	# Of papers/reports
Multiple sclerosis	16
Psoriasis	5
Systemic lupus erythematosus	5
Diabetes insipidus	3
Hyperparathyroidism	3
Autoimmune hemolysis	2
Diabetes mellitus type 1	2
Ulcerative colitis	2
Alopecia areata	1
Autoimmune thyroiditis	1
Common variable immunodeficiency	1
Hashimoto's thyroiditis	1
Mixed connective tissue disease	1
Monoarticular juvenile arthritis	1
Vitiligo	1
Sum	45

What is biome depletion theory?

Strachan is credited with expounding on a theory currently referred to as the "Hygiene Hypothesis," which posits that family size, birth order and exposure to infection seem to mitigate the development of allergic and atopic diseases [27].

The Hygiene Hypothesis concept has since been expanded upon by Rook, who has advanced the term "Old Friends Theory" to describe current understanding. Rook posits that exposure to *particular* classes of organisms, such as saprophytic bacteria and select helminths, both once ubiquitous in the environment prior to widespread public health measures, may have an immunomodulatory effect on the human immune system [28]. Replenishment of these organisms in humans may potentially reduce the incidence and severity of allergic and autoimmune diseases.

It is opined herein that the term "Biome Depletion Theory" is a somewhat more descriptive term than "Old Friends Theory," and therefore although the two suppositions have much overlap, it is the term employed herein.

"Biome Depletion Theory" is a descriptor used by Bilbo et al. [29]. It is generally accepted that the human body is a total ecology comprised of a plethora of commensal and mutualistic organisms and indeed it cannot function without them. For example, the synthesis of vitamins by certain forms of gut bacteria is necessary for human survival.

The microbiome is becoming an important area of study. However, it is also coming to be recognized that macrobiotic organisms, such as helminths, may also be critical to proper immune function [30]; therefore, the term "biome" more accurately describes the entirety of the human internal ecology. The absence, or "depletion," of critical organisms within the biome, is thought to result in chronic inflammation and disease.

Biome Depletion Theory further encompasses the concept of "Evolutionary Mismatch," a term that predates WWI, and reflects the inability of the human body to adapt to rapid environmental changes. One of the most notable of these recent environmental alterations has been the removal of what are presently thought by some to be mutualistic organisms, brought about by factors such as modern sanitation, multi-generational antibiotic usage, and changes in breastfeeding practices. In what Weinstock describes as a mathematically "perfect correlation," a concurrent increase in autoimmune states has occurred, possibly as a result