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Commentary on the Practice of Medicine (9): The Symphony of Genes

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AWAKENING THE POWER OF THE NEW HUMAN STORY

The widely known Indian-American author, Deepak Chopra, a reference in alternative medicine, referred to Gregg Braden as "a rare blend of scientist, visionary and scholar with the ability to speak to our minds while touching the wisdom of our hearts" [1]. I very much admire people like Gregg Braden who are able to blend spiritual issues with "scientifically proven knowledge", awakening people to move forward in their own paths to reach higher levels of understanding or, else, simply living in deeper peace and harmony. According to him, new discoveries reveal new potentials, new capabilities, new ways of looking into the mystery of one another [1]. Before him, in 1944, the Indian Hindumonk, yogi and guru Paramahansa Yogananda (1893 - 1952) wrote the book "The Law of Success: using the power of the spirit to create health, prosperity and happiness" [2], which has a similar line of thought. My point is: if many doctors started to make the connection between thoughts, emotions, beliefs and gene expression, we would inevitably be creating a new practice of western medicine, very different from the drug- based therapeutical approach we learned during our medical courses. But things don't change from one minute to another. It is, indeed, a slow process. However, some people may pay the price for being pioneers in certain emerging fields of research. I believe that is sort of what is happening to me. I was accused again of violating the article 35 of the Brazilian Code of Medical Ethics. Article 35: The doctor is prohibited from exaggerating the severity of the diagnosis or prognosis, complicating the therapy or exceeding the number of visits, consultations or any other medical procedures". To be honest, so far I didn't understand the precise correlation between the article 35 and the accusation. Just because I said I do not depend on the "names" given to diseases to treat my patients: I will always treat them with supplements, such as vitamins, minerals, amino acids, essential fatty acids, and herbal medicines. Nowadays, whenever possible, I very much rely on the information I get from the patient's nutrigenomics panel to choose more assertively which substances and doses to prescribe. In this article I will try to make it clear why I think that differential diagnosis of diseases is much more complex than what we have ever thought. Needless to say that we are not talking about straightforward diagnoses, such as traumas, fractures and infections, but to more complex chronic conditions.

THE SYMPHONY OF GENES

I have been learning more about gene expression since 2017. It started to become clear to me that we have thousands of genes which work like members of a symphonic orchestra. At a particular moment, some are playing with a lot of "pressure" on them: they are the main players, calling most of the attention over themselves. But some are relatively in the background, while some may not be playing at all. However, it all changes along the time: some musicians may start to play a more outstanding role, others may continue to play, though more in the background than before, and others may go silent for a while. Regardless of anything, the orchestra carries on playing melodies with different compositions of members and instruments. In my view,the genes work in a similar way, expressing themselves either strongly, either weakly or they may just be turned "off". At a certain moment, the expression of some genes may be so strong that it makes it easier to give a definite diagnosis of a disease. Even so the symphony of genes goes on and on playing endlessly. Unfortunately, some patients might carry the burden of having a particular disease for the rest of their lives. The diagnosis was given like a life sentence. All in all, the way I see it, disease names are like spotlights over someone during a musical play while there are many others taking part in the scene at the same time.

AN ILLUSTRATIVE CASE

We do know that we have thousands of genes. Each of them

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may express themselves in different ways or may not express themselves at all. This is because different epigenetic processes have influence on them, such as DNA methylation, histone modifications and noncoding RNAs [3] **(Figure 1)**.

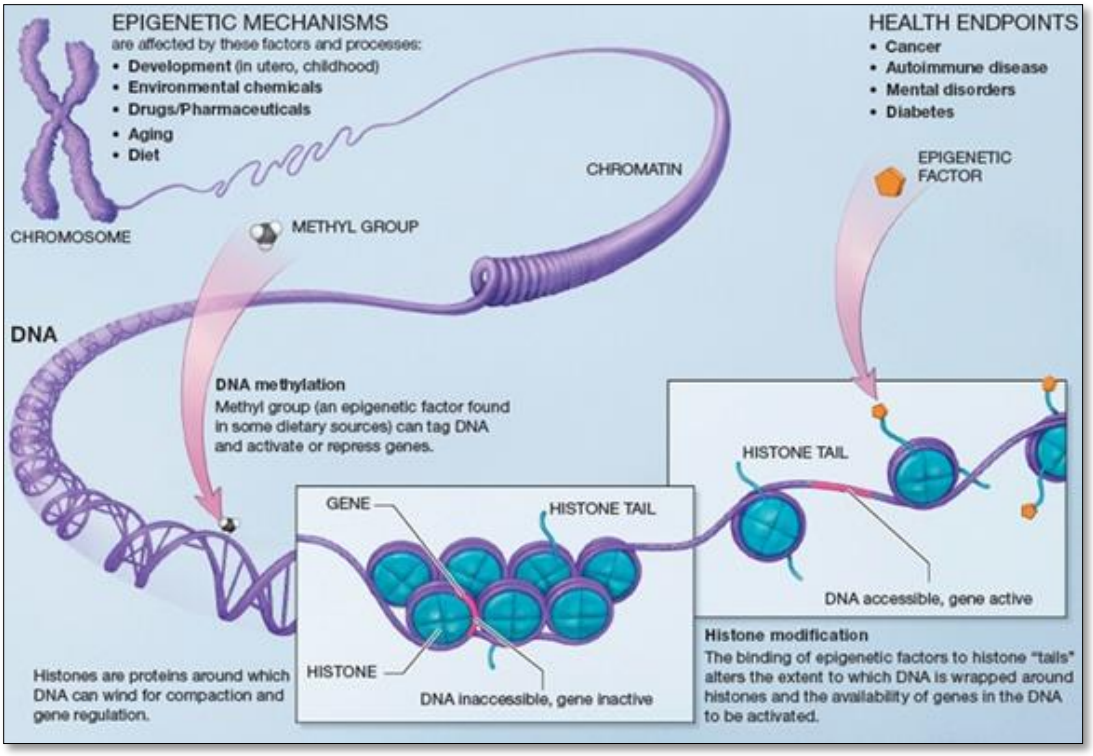

Figure 1. An Illustration of How Epigenetic Mechanisms Can Affect Health [4].

Figure 1 [4] shows the relationship between epigenetic mechanisms, epigenetic factors, epigenetic processes and health endpoints. Notice that we have DNA inaccessible (gene inactive) and DNA accessible (gene active). I consider that this understanding is one of the most important achievements in the XXI century as far as health maintenance and prevention of diseases are concerned. Moreover, it is great that we can actually interfere on DNA methylation with nutrients/methyl donors and co-factors, such as methylfolate, methylcobalamin, methionine, choline, betaine, pyridoxine, riboflavine and others. Considering all this knowledge, suppose we have a patient with frontotemporal dementia: a dementia caused by degeneration of the frontotemporal lobe and clinically associated with personality and behavioral changes such as disinhibition, apathy, and lack of insight [5]. The hallmark feature of frontotemporal dementia is the presentation with focal syndromes, such as progressive language dysfunction, aphasia, or behavioral changes characteristic of frontal lobe disorders [5]. Nonetheless, the same patient was previously given the diagnosis of amyotrophic lateral sclerosis (ALS), a neurodegenerative disorder affecting primarily the motor system, but in which extra-motor manifestations are increasingly recognized [6]. According to a review article published in 2020, in up to 50% of cases there are extra-motor manifestations, such as changes in behavior, executive dysfunction and language problems [6]. In 10%-15% of patients these problems are severe enough to meet the clinical criteria of frontotemporal dementia (FTD) [6]. Therefore, it seems that our patient has ALS with associated frontotemporal dementia. Nevertheless, can we be 100% sure that his dementia is only related to ALS? Have a look on **Table 1** [6]. What if, for instance, the genes CHCHD10, DCTN1 and VCP are involved? They are connected with many diseases, including ALS. Can we say that the patient's dementia has components of other known diseases? On the other hand, can you see that the "name" given to a disease is just a name when you work with genes? The more we know about genes, the more we realize that, in general, we should not give only one and definite diagnosis to more complex chronic conditions. The Human Phenotype Ontology (HPO) site makes the correlation between gene symbols and associated diseases in frontotemporal dementias [6], as shown below. The sources of information are Orphanet (ORPHA) [7], an online database to gather, provide and improve knowledge, diagnosis, care and treatment on rare diseases and Online Mendelian Inheritance in Man (OMIM) [8], a comprehensive, authoritative compendium of human genes and genetic phenotypes.

Table 1. Genes and associated diseases in frontotemporal dementias [6].

Gene symbol	Associated Diseases
ABCA7	(ORPHA:1020) - Early-onset autosomal dominant Alzheimer disease(OMIM:608907) - Alzheimer disease 9, susceptibility to
APP	(ORPHA:100006) - ABeta amyloidosis, Dutch type(OMIM:104300) – Alzheimer disease (ORPHA:324723) - ABeta amyloidosis, Arctic type (ORPHA:324703) - ABetaL34V amyloidosis (ORPHA:324708) - ABeta amyloidosis, Iowa type (ORPHA:324713) - ABeta amyloidosis, Italian type (ORPHA:1020) - Early-onset autosomal dominant Alzheimer disease(OMIM:605714) - Cerebral amyloid angiopathy, APP-related
C9orf72	(OMIM:105550) - Amyotrophic lateral sclerosis and/or frontotemporal dementia 1
CCNF	(ORPHA:803) - Amyotrophic lateral sclerosis (OMIM:619141) - Frontotemporal dementia and/or amyotrophic lateral sclerosis 5
CHCHD10	(ORPHA:457050) - Autosomal dominant mitochondrial myopathy with exercise intolerance(ORPHA:275872) - Frontotemporal dementia with motor neuron disease (OMIM:615911) - Frontotemporal dementia and/or amyotrophic lateral sclerosis 2(ORPHA:803) - Amyotrophic lateral sclerosis (OMIM:615048) - Spinal muscular atrophy, Jokela type (ORPHA:276435) - Lower motor neuron syndrome with late-adult onset (OMIM:616209) - Myopathy, isolated mitochondrial, autosomal dominant
CHMP2B	(ORPHA:100070) - Progressive non-fluent aphasia(ORPHA:803) - Amyotrophic lateral sclerosis (OMIM:600795) - Frontotemporal dementia and/or amytrophic lateral sclerosis 7(ORPHA:275864) - Behavioral variant of frontotemporal dementia (ORPHA:100069) - Semantic dementia
CYLD	(ORPHA:211) - Familial cylindromatosis (OMIM:605041) - Brooke-Spiegler syndrome (ORPHA:867) - Familial multiple trichoepithelioma (OMIM:619132) - Frontotemporal dementia and/or amytrophic lateral sclerosis 8(OMIM:601606) - Trichoepithelioma, multiple familial, 1 (OMIM:132700) - Cylindromatosis, familial
DCTN1	(OMIM:168605) - Perry syndrome (OMIM:105400) - Amyotrophic lateral sclerosis 1(ORPHA:803) - Amyotrophic lateral sclerosis (OMIM:607641) - Neuronopathy, distal hereditary motor, type VIIB(ORPHA:178509) - Perry syndrome
FUS	(ORPHA:275872) - Frontotemporal dementia with motor neuron disease (OMIM:608030) - Amyotrophic lateral sclerosis 6, with or without frontotemporal dementia(ORPHA:803) - Amyotrophic lateral sclerosis (OMIM:614782) - Tremor, hereditary essential, 4 (ORPHA:99967) - Myxoid/round cell liposarcoma (ORPHA:300605) - Juvenile amyotrophic lateral sclerosis
GRN	(ORPHA:100070) - Progressive non-fluent aphasia (OMIM:614706) - Ceroid lipofuscinosis, neuronal, 11 (ORPHA:275864) - Behavioral variant of frontotemporal dementia(ORPHA:100069) - Semantic dementia (OMIM:607485) - Frontotemporal lobar degeneration with TDP43 inclusions
HNRNPA1	(ORPHA:803) - Amyotrophic lateral sclerosis (ORPHA:52430) - Inclusion body myopathy with Paget disease of bone and frontotemporal dementia (OMIM:615424) - Inclusion body myopathy with early-onset Paget disease without frontotemporal dementia 3(OMIM:615426) - Amyotrophic lateral sclerosis 20
HNRNPA2B1	(ORPHA:52430) - Inclusion body myopathy with Paget disease of bone and frontotemporal dementia (OMIM:615422) - Inclusion body myopathy with early-onset Paget disease with or without frontotemporaldementia 2
MAPT	(OMIM:601104) - Supranuclear palsy, progressive, 1(ORPHA:100069) - Semantic dementia (OMIM:260540) - Supranuclear palsy, progressive atypical (ORPHA:240094) - Progressive supranuclear palsy-pure akinesia with gait freezing syndrome(ORPHA:240112) - Progressive supranuclear palsy-progressive non-fluent aphasia syndrome(ORPHA:240103) - Progressive supranuclear palsy-corticobasal syndrome (ORPHA:240085) - Progressive supranuclear palsy-parkinsonism syndrome(ORPHA:275864) - Behavioral variant of frontotemporal dementia (OMIM:600274) - Frontotemporal dementia (ORPHA:100070) - Progressive non-fluent aphasia(OMIM:172700) - Pick disease of brain (ORPHA:240071) - Classic progressive supranuclear palsy syndrome(OMIM:168600) - Parkinson disease, late-onset
PLA2G6	(OMIM:612953) - Parkinson disease 14, autosomal recessive(ORPHA:35069) - Infantile neuroaxonal dystrophy (OMIM:256600) - Neurodegeneration with brain iron accumulation 2A(ORPHA:199351) - Adult-onset dystonia-parkinsonism (OMIM:610217) - Neurodegeneration with brain iron accumulation 2B
PRKAR1B	(ORPHA:412066) - PRKAR1B-related neurodegenerative dementia with intermediate filaments(OMIM:619680) - Marbach-Schaaf neurodevelopmental syndrome
PSEN1	(OMIM:607822) - Alzheimer disease 3 (ORPHA:154) - Familial isolated dilated cardiomyopathy(OMIM:613694) - Cardiomyopathy, dilated, 1U (ORPHA:100069) - Semantic dementia (OMIM:172700) - Pick disease of brain (OMIM:613737) - Acne inversa, familial, 3 (ORPHA:275864) - Behavioral variant of frontotemporal dementia (ORPHA:1020) - Early-onset autosomal dominant Alzheimer disease(OMIM:600274) - Frontotemporal dementia

	(ORPHA:100070) - Progressive non-fluent aphasia
PSEN2	(OMIM:606889) - Alzheimer disease 4 (ORPHA:154) - Familial isolated dilated cardiomyopathy(OMIM:613697) - Cardiomyopathy, dilated, 1V (ORPHA:1020) - Early-onset autosomal dominant Alzheimer disease
SORL1	(ORPHA:1020) - Early-onset autosomal dominant Alzheimer disease
SQSTM1	(OMIM:167250) - Paget disease of bone 3 (OMIM:617145) - Neurodegeneration with ataxia, dystonia, and gaze palsy, childhood-onset(ORPHA:275872) - Frontotemporal dementia with motor neuron disease (ORPHA:803) - Amyotrophic lateral sclerosis (OMIM:616437) - Frontotemporal dementia and/or amyotrophic lateral sclerosis 3(ORPHA:603) - Distal myopathy, Welander type (ORPHA:275864) - Behavioral variant of frontotemporal dementia(OMIM:617158) - Myopathy, distal, with rimmed vacuoles
TARDBP	(ORPHA:275872) - Frontotemporal dementia with motor neuron disease(ORPHA:803) - Amyotrophic lateral sclerosis (OMIM:612069) - Amyotrophic lateral sclerosis 10 with or without frontotemporal dementia
TBK1	(OMIM:616439) - Frontotemporal dementia and/or amyotrophic lateral sclerosis 4(ORPHA:275872) - Frontotemporal dementia with motor neuron disease (ORPHA:803) - Amyotrophic lateral sclerosis (OMIM:617900) - Encephalopathy, acute, infection-induced (herpes-specific), susceptibility to, 8(ORPHA:1930) - Herpes simplex virus encephalitis
TIA1	(ORPHA:603) - Distal myopathy, Welander type(OMIM:604454) - Welander distal myopathy (OMIM:619133) - Amyotrophic lateral sclerosis 26 with or without frontotemporal dementia
TMEM106B	(ORPHA:100069) - Semantic dementia (OMIM:617964) - Leukodystrophy, hypomyelinating, 16 (ORPHA:275864) - Behavioral variant of frontotemporal dementia(ORPHA:100070) - Progressive non-fluent aphasia
TOMM40	(ORPHA:1020) - Early-onset autosomal dominant Alzheimer disease
TREM2	(ORPHA:100069) - Semantic dementia (OMIM:618193) - Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy 2(ORPHA:803) - Amyotrophic lateral sclerosis (ORPHA:275864) - Behavioral variant of frontotemporal dementia (ORPHA:1020) - Early-onset autosomal dominant Alzheimer disease(ORPHA:2770) - Nasu-Hakola disease (ORPHA:100070) - Progressive non-fluent aphasia
TUBA4A	(OMIM:616208) - Amyotrophic lateral sclerosis 22 with or without frontotemporal dementia
UBQLN2	(OMIM:300857) - Amyotrophic lateral sclerosis 15 with or without frontotemporal dementia(ORPHA:803) - Amyotrophic lateral sclerosis
VCP	(ORPHA:435387) - Autosomal dominant Charcot-Marie-Tooth disease type 2Y (ORPHA:329478) - Adult-onset distal myopathy due to VCP mutation (OMIM:613954) - Frontotemporal dementia and/or amyotrophic lateral sclerosis 6(ORPHA:329475) - Spastic paraplegia-Paget disease of bone syndrome (OMIM:167320) - Inclusion body myopathy with early-onset paget disease with or without frontotemporaldementia 1 (ORPHA:275872) - Frontotemporal dementia with motor neuron disease(ORPHA:803) - Amyotrophic lateral sclerosis (ORPHA:275864) - Behavioral variant of frontotemporal dementia(OMIM:616687) - Charcot-Marie-Tooth disease, axonal, type 2Y (ORPHA:100070) - Progressive non-fluent aphasia (ORPHA:52430) - Inclusion body myopathy with Paget disease of bone and frontotemporal dementia
ZFYVE26	(ORPHA:100996) - Autosomal recessive spastic paraplegia type 15(OMIM:270700) - Spastic paraplegia 15, autosomal recessive

AHEAD OF TIME?

In 1982 I was preparing myself to go to university. I wasn't sure about what to do. My father was a doctor himself and I asked him if he could help me somehow on my decision. He suggested me to work with Preventive Medicine, the medicine of the future, as he said. At the time I had no idea of what he was talking about. For sure it didn't have any glamour connected to it. If he had proposed me Genomic Medicine, I believe it would have sounded more impressive. Nonetheless the Genome Project only started in 1990 [9]. So, my father may be considered ahead of his time. In my case, I was accused of violating the Brazilian Code of Medical Ethics just because I believe that differential diagnosis will not be necessary in the foreseeable future. At least not in the same way we are used to. Anyway, it was not an "official" statement, that is, I didn't publish it anywhere or tried to convince someone of my own perception. It was just my point of view, regrettably mentioned to some colleagues, medical doctors as well. In the 5th article of this series, I wrote that I treated a patient with amyotrophic lateral sclerosis in the same way I do with all my patients, prescribing to him protection against inflammation, oxidation, glycation, acidification and sub-methylation, all of which are processes related to molecular damage, aging and diseases in the long run. His daughter came to my office because it was necessary the prescription of a nutritional supplement by a physician to get it from the public health care system and I felt I could contribute with more than what she asked me to do. In the end he lived another five or six years with much better quality of life than when we first met.

All in all, I work alone and my approach is focused on preventive care and it is certainly much easier not to need “names" for diseases than if I worked in a hospital with serious cases and sharing the patients with all the staff, doctors and nurses.

THE BLOSSOMING

In my appointments with patients I briefly talk about the awakening for a new human history, as proposed by Gregg Braden, trying to open this door to the “new" information that is blossoming like a spring flowery tree. No doubt positive thoughts and emotions can help the patients to find their own paths of cure or, at least, try to. Also, in order to make them aware of the importance of being proactive towards health, I explain to them the recent knowledge about neuroplasticity, defined as the ability of the nervous system to change its activity in response to intrinsic or extrinsic stimuli by reorganizing its structure, functions, or connections [10]. We now know it is possible to create “new brain” by forming neural pathways throughout life and in response to experiences [11]. While the brain usually does this itself in response to injury or diseases, when humans focus their attention enough, they can slowly rewire these pathways themselves [11]. In other words, we realize that we can literally make ourselves a better brain [12]. According to Norman Doidge in his book “The brain that changes itself”: "If we only strengthened connections, our neuronal networks would get saturated. Evidence suggests that unlearning existing memories is necessary to make room for new memories in our networks. Unlearning is essential when we are moving from one developmental stage to the next” [12]. In short, a lot of the processes of cure are dependent upon our own everyday efforts to improve ourselves by consciously changing our brain: making new “good" connections while unlearning some “negative" memories at the same time.

FRAMELESS HEADS ON NAMELESS WALLS

I was listening to "Vincent”, wonderful song by Don McLean [13]. When I heard "they would not listen, they did not know how, perhaps they'll listen now”, I made the connection between the words and my own "drama", if I can put it that way. During years of accusations, they would never listen to me and perhaps they will listen now. And I do hope they will. One day I may be forgotten like "a frameless head on a nameless wall”, as in the lyrics of "Starry, starry night”. However, may the intention remain: to draw attention to an issue that has been going on in the medical world and growing along the time: disrespect for the individuality, suppression of freedom, incomprehension that there are different approaches towards health and that not only the doctors themselves but, also, the patients should have the right to choose their own ways. Let’s make something constructive out of it. With love and glory.

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