

Home Genomics



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Abstract

Introduction: The application of personalized medicine in the medical practice requires the study of the human genome with regard to drugs pharmacokinetics, pharmacodynamics, interactions and tolerance profile. The consideration of gene × environment interactions and the inclusion of “omics” data in pharmacogenomic studies of drugs will facilitate the generation of reliable results and will promote tailored treatments and new strategies of research and development. Pharmacogenetics is the search for genetic polymorphisms that affect responses to drug therapy and refers to the study of variations in a single gene, whereas pharmacogenomics is the study of variations in multiple genes and the basis of personalisation of treatment to allow higher medication success rates. Homeogenomics should focus on homeopathic remedies since Homeopathy is a personalized and holistic healing method.

Objective: This article proposes a philosophical–scientific correlation between homeopathic remedies and epigenetic modifications as homeopathic medicine being also a modulator of gene expression.

Results: Based on the study of homeopathic doctrine and epigenetics, a conceptual and functional correlation is observed between homeopathic remedies and epigenetic modifications. Several experimental studies suggest that homeopathy’s mechanism of action may be by modulating gene expression.

Conclusions: According to modern genetics, epigenetic alterations are the fundamental cause of the manifestation of chronic diseases as well as therapeutic modulator of gene expression for their management. Homeopathic remedies may act on the epigenetic expression of the individual to heal personally and holistically.

Keywords: Homeopathy; Epigenome; Environment interactions; Gene interactions; Genome; Omics; Personalized medicine; Pharmacogenomics

Introduction

Genetics has historically focused on chromosomal and metabolic disorders through the window of relatively rare single gene diseases., but it is well understood that genetic background plays a main role in every medical condition such as hypertension, asthma, diabetes, but particularly in disease susceptibility, the interaction with the environment, host responses to illness and to pharmaceutical agents, and metabolic drugs as evident from the patient’s family history. The basic purpose of genes is the production of structural proteins and enzymes through a series of events, termed transcription, processing, and translation. Medical genetics is concerned with the study of human genetic variation whose basis is mutation or change in the DNA sequence. Mutations can occur in every cell of the body: When they occur in somatic cells, there is a risk of cancer development; in the germ line, the risk is a structural or functional disability.

Pharmacogenetics and pharmacogenomics involve the search for genetic polymorphisms that influence responses to therapy. These disciplines offer the opportunity to provide individualized therapy on the basis of a person’s genetic makeup limiting adverse effects. Molecular biological technologies confirmed that highly diluted substances such as plant and tissue extracts have the capacity to boost gene expression in a specific way. Homeopathy is usually considered placebo treatment because of the extremely low doses used. Dynamic and extremely low attenuated homeopathic remedies must have the capacity to promote changes in gene activity and to stimulate the genetic code by activation or deactivation of specific genes that synthesize the proteins such as enzymes, hormones and inflammatory mediators [1-3]. The physical nature of homeopathic remedies and the precise role of succession in the remedy preparation process are still unknown. Studies from several independent laboratories have indicated

enhanced cellular adaptive process and anticancer effects with low doses of chemicals including some homeopathy medicines [4]. Similarly, ultralow doses of cadmium have been shown to induce the expression of protective proteins and render the protection of prostate cells from neoplastic transformation to higher dose exposures [5,6]. Arsenic trioxide has been widely used in homeopathic medicine and has been shown to induce incomplete differentiation, apoptosis, and degradation of oncogenic protein in acute promyelocytic leukemia [7].

Ultra-low doses of TNF and adriamycin/cisplatin have been reported to induce apoptosis in resistant human ovarian cancer cells [8]. Immunotherapy of hepatocellular carcinoma patients using an ultralow dose of IL-2 (1 MIU/d) induced tumor regression and prolonged the patients' survival [9]. The toxicity of ultrahigh dilutions of 3,5-dichlorophenol showed a significant inhibitory effect from these preparations using luminescent bacteria testing [10]. Analyses of reports from clinical trials of homeopathy mostly address the clinical effects of homeopathic medicines, and not their mechanisms of action [11]. Investigation of homeopathic treatment requires novel and sensitive methodologies such as global gene array analysis to detect subtle differences for the beneficial effects of homeopathic treatment in vivo [12]. Homeopathic medicine triggers a reaction against the pre-existing organic disturbance and removes the signs and symptoms by means of symptomatic therapeutic similitude. By presenting conceptual and functional similarities, the homeopathic remedies find their biological representation in epigenetic modifications [13].

Life, Vitality, DNA, and Epigenome

Every living organism, from the simplest form to the most complex one, presents biochemical information that allows it to function, develop, and multiply. DNA stores and replicates this information from one generation to another and undergoes adaptive mutations to adjust to different environmental conditions by natural selection. DNA, genetic material, or genome consists of a set of sequences of nucleotides, molecules consisting of phosphate, deoxyribose, and a nitrogenous base (adenine, thymine, cytosine, or guanine). Each specific nucleotide sequence, which generates a protein-encoding gene, is called an exon. The set of exons, in other words the encoding part of the genome, is called the exome [14].

The Human Genome Project highlighted that only 1 to 2% of the three billion genome nucleotide sequences are responsible for 20,000 to 25,000 protein-encoding genes (encoding DNA or exome), while the genetic material left (98%) consists of noncoding DNA. They also verified that the same nucleotide sequence (genes) generates hundreds of cell types and dozens of different tissues, thus bringing down the key molecular biology dogma, according to which the production of protein would be limited to a single sequence of events. Thus, there is another

genetic control mechanism that regulates gene expression, known as 'epigenetics' (from the Greek prefix, epi, 'above', 'on' or 'beyond'), established in 1942 by British embryologist and geneticist Conrad H. Waddington. The human body consists of close to one hundred trillion cells that come from a single egg-cell or zygote (fusion of gametes' DNA), which replicates the same genome for other cells following the signals captured from within the very cells (cytoplasm), neighboring cells, and from the environment. Stimuli reaching the nucleus will determine the morphology, physiology, and behavior of the future embryo and individual. The cells respond to different signals and stimuli, both environmental and physical (temperature, pollutants, nutrients, hormones and medicines) and behavioral (lifestyle, stress, emotions and feelings).

The human DNA molecule (if stretched, roughly 2 m long, while the human cell nucleus is 5 μm) is rolled with nuclear proteins called histones in nucleosomes. If DNA was fully enveloped, the genes would not be able to decode their base sequence in the form of protein. That is why the DNA molecule is partially unwrapped making genes accessible to the action of transcription factors to be expressed by the arrival of signals and stimuli. Genes are located in different regions of DNA molecules. are expressed at various moments. Parts of DNA molecules are constantly unrolled and rolled back (chromosome or chromatin remodeling) because of epigenetic modifications due to chemical changes occurring in the DNA molecule and histone proteins. There are more than 100 epigenetic modifications or alterations that can affect chromatin. In DNA methylation process, a methyl group (-CH₃) is added to the cytosine nucleotide; both the methylation and acetylation (-COCH₃) processes of the lysine and arginine amino acids can occur in the histone. The modifications in the DNA and in the histones are performed by enzymes of the following types: DNA methylase/demethylase, histone methylase/demethylase, and histone acetylase/ deacetylase. DNA methylation process causes chromatin wrapping in regions that control gene expression (called 'promoters'), and results in silencing of genes because methylated genes do not encode proteins. The histone acetylation process is related to the unwrapping of chromatin and gene activation [15].

The term epigenetic means additional information to the genetic information encoded in DNA, and defines gene expression modifications, without any change in the genetic code of the nucleotide sequence. The epigenetic modifications, or epigenome, can be considered as a set of chemical processes forming an additional layer of gene expression regulation at transcriptional level, that modify the genome functions and phenotypic profile, by activating or deactivating genes. Each tissue presents a distinct epigenome with specific epigenetic modifications manifested in healthy or sick development. Encoding (exome) and non-encoding (epigenome) portions of the genome regulate the encoding process [5]. Epigenetic modifications can be expressed in the genome

of individuals at any age, when they contact promoting agents by either activating or silencing the genes. Disease-promoting epigenetic modifications can be reversed by promoting their re-programming (epigenetic modulation) [16].

The epigenome (set of epigenetic alterations or chemical modifications inserted in the genome and the chromatin) can be passed on to descendant cells, maintaining a specific epigenetic pattern (epigenetic code or epigenotype) for generations [17]. The health–disease correlation of the descendants is called epigenetic susceptibility. The phenotype becomes the outcome of not just the genotype but of the epigenotype as well, allowing added gene expression control, which shows as much plasticity as the genotype. The epigenetic code gives the order to the genome when and where and which genes will be expressed. The expression of the epigenetic alterations on the genome is affected by external and internal environmental factors, such as lifestyle and habits, irradiation and pollution, hormones, medicines, inflammation, hypoxia, stress, emotional and psychic aspects. During pregnancy, for instance, harmful factors can influence the embryo's epigenetic mechanisms, and increase the risk of future development of a number of disorders and diseases such as obesity, diabetes, hypertension, depression, attention deficit hyperactivity disorder and schizophrenia [8]. Homeopathic remedies act on the Genome by modulating gene expression. Scientific evidence based on experimental studies, since 1997, have shown the effects of homeopathic medicine on repairing chromosome damage caused by toxic or radioactive stimuli, by regulating gene expression at one or more levels of control [11]. The results of many homeo genetic studies confirm the postulate that 'homeopathic remedies could deliver their benefits by interacting with the genetic blueprint', including 'epigenetic modifications such as DNA methylation'. Homeopathic remedies would have the capacity to interact with the genome and rearrange the expression of many genes' [18].

In an article that summarizes the results of in-vitro and animal studies showing how molecular biological tools can provide useful suggestions about how human organisms behave when treated with homeopathic medicine, the authors suggest that the action of homeopathic remedies proceed through modulation of gene expressions [19]. In another review, Bellavite et al describe experiments that show the action of homeopathic medicine on gene expression, and support the hypothesis that homeopathic remedies could turn genes on or off, initiating a cascade of gene actions to correct the gene expression that has gone wrong and produced a disorder or disease and act at gene regulatory level according to three main types of effects: change in the expression pattern of many genes, cytotoxicity or apoptosis in cancer cells, and therapeutic modification in gene expression. DNA extracted from whole blood or specific tissue sample (auto-sarcode of specific DNA), would be acting on the epigenome systemic modulation, to restore the organism's dynamic, complex, and

global balance, either associated or not with chronic diseases and enhance the response by directing gene modulation toward epigenetic modifications located in particular tissues, manifesting specific chronic diseases [20].

According to mechanistic models, science has assumed that everything was a series of chemical reactions, where proteins act in a series of physical lock and key interactions, and DNA is housed in the nucleus of the cell with the genes coded for the chemicals of life. If genes have not been irrevocably damaged, they are capable of being switched on and off according to interactions with a multitude of factors, including diet and environmental changes. Over 25,000 genes code for the more than 100,000 proteins that make up the material of life. The mainstream conventional scientific world is changing its perspective. Researchers are currently able to measure changes occurring at the level of genetic switching. Homeopaths may now be able to measure and, "observe" the action of a dynamic remedy generating a change in the living body that becomes material through molecular biological tools, such as DNA-microarrays and the ability to utilize specific cell line cultures. A greater understanding of the hormesis concept (dose-response relationship that shows how substances can be either inhibitory or stimulatory at different dose rates) challenges the way conventional pharmacology has evaluated drug dose rates. Considering the same substance given to inhibit or stimulate a body response, the use of therapeutic microdoses would be calculated according to the genetic makeup of the individual receiving the dose [21].

A significant number of studies have shown a positive response

One study looked at the gene expression of RWPE-1 cells (prostate epithelial cells) when exposed to *Apis mellifica* (a well-known remedy to homeopaths, made from the honeybee, including the venom) mother tincture. — 3C, 5C and 7C potencies for 24 hours. This remedy is used for many different presentations of allergy – edema, redness, pain and inflammation. The researchers looked at the expression of genes involved in cytokine expression, inflammatory processes, anti-oxidative responses and protease degradation and found that the mother tincture increased expression of the IL1b gene, which codes a potent pro-inflammatory cytokine, whereas the potentised remedies reduced expression of the same gene [22].

A number of studies have looked at *Gelsemium sempervirens* and gene expressions. Bellavite et al exposed human SH-SY5Y cells (neuroblastoma cells) to potentised dilutions of *Gelsemium* (2C, 3C, 4C, 5C, 9C and 30C) for 24 hours and found that the expression of 56 genes was significantly changed (49 down-regulated and seven up-regulated). *Gelsemium sempervirens* has long been recognised by homeopaths as having its centre of action on the nervous system and muscles. The plant from which the remedy is derived contains strychnine-like alkaloids, such as gelsemine, that act within this sphere. The authors suggest that the pain-relieving

and anti-anxiety effects associated with the remedy may be attributed to the negative modulation of some neuronal excitatory signaling pathways [23].

Using microarray and RT-PCR techniques, Preethi et al investigated the expression of genes associated with cytotoxicity and apoptosis (programmed cell death) in Dalton's lymphoma tumor cells and other tumor cell lines. They exposed the cells to ten different potentised medicines, including Ruta 200C, Carcininum 200C, Hydrastis 200C, Conium 200C, Podophyllum 200C and Thuja 200C and found different effects in different remedies with different potencies. Conium 200C was more cytotoxic than its mother tincture; Carcininum was more cytotoxic at 200C than at 30C. The researchers were able to demonstrate clear gene induction in some cases — Carcininum 200C significantly induced p53 gene expression (pro-apoptotic gene) [24].

Khuda-Bukhsh et al used HeLa cells (HPV18 positive cells) to test the effects of the ultra-high dilutions Condurango 30C and Hydrastis canadensis 30C on gene expression when compared to controls. They were able to demonstrate significantly different gene expression patterns of genes associated with carcinogenesis for the ultra-high dilutions, when compared to controls. Hydrastis canadensis and Condurango are both commonly used as homeopathic remedies in cancer cases. Classical homeopath Clarke cited Hydrastis as the remedy that has cured more cases of cancer than any other single remedy [25]. Homeopathically prepared DNA taken from a variety of sources (eg. fish and cattle) has had a number of provings over the years and has been found to have affinities with the mind, nerves, endocrine and reproductive systems [26]. Sequence Specific Homeopathic DNA remedies which use specific DNA sequences (300 to 400 base pairs in length) potentised to 6 C have been used at targeting genes known to have suboptimal expression in certain disease states or processes [27].

Dr Batra's Geno Homeopathy consists of Precise gene-targeting for exact diagnostic evaluation; is Painless and natural; and offers Personalized treatment plans based on unique genetic history of a patient. It Predicts the likelihood of genetic ailments well before symptoms appear and also attempts to Prevent the risk of any hereditary illnesses through timely treatment. The Genetic Test for Dr Batra's Geno Homeopathy consists of a simple saliva test that can assess the severity of a medical problem even years before the disease appears. Dr Batra's medical experts in conjunction with specialists in genomics have designed a Genetic Test which includes an extensive list of 15 markers per test as per individual ailments and comprise of all related problems to the main condition or complaint including primary and secondary problems. Ailments covered include Hair loss, Psoriasis, Acne, Vitiligo, Skin and Respiratory Allergies, Child Health, Weight Management, Stress, Preventive and Women's Health. They indicate the gravity of the illness and give an in-depth analysis of the condition. The Genetic Test also provides patients with a lifestyle chart that incorporates dietary and exercise programs to

complement the treatment plan.

Having launched Geno Homeopathy in India in 2018, Dr Batra's has conducted over 15,000 Geno Homeopathy tests. From the over 1,000,000 patients that have opted for Homeopathic treatment at Dr Batra's and have seen 91% successful patient outcomes as authenticated by American Quality Assessors, over 500 patients have seen further enhanced treatment outcomes from their Geno Homeopathy treatment. Dr Batra's has partnered with GeneStore which provides genetic testing in over 10 countries and has conducted over 500,000 genetic tests worldwide. The GeneStore's genetic laboratories are based in U.S.A., UAE, Uruguay, India and France.

The results have also indicated

With most ailments today being lifestyle related, over 45% of patients diagnosed with underlying ailments, benefitted purely through diet and nutrition corrections. 17% of patients identified underlying complications that they were unaware of and received timely intervention that led to better patient outcomes. Patients tested for hair loss, 74% men and 71% women were prone to diabetes, while 79% men and 74% women were at risk of hypothyroidism. At Dr Batra's they got treated for both hair loss and diabetes/hypothyroidism. Through Dr Batra's genetic tests for Geno Homeopathy, patients with a family history of psoriasis can predict their likelihood of developing the ailment even before the symptoms begin to appear. By accurately predicting the hidden ailment, Dr Batra's Geno Homeopathy will provide preventive treatment not just for the ailment but also for related issues like Psoriatic Arthritis, Nutritional deficiencies, Hypothyroid, Stress and Insulin Resistance [28].

Conclusion

Personalized and holistic medical approach has started to use pharmacogenetics through detecting genetic profile from a simple saliva test. In this way, the trend is to detect disease susceptibility of the person, predict and prevent the potential disease and treat if the disease already manifested. Homeopathy is a widely used medical method which already approaches the person as an individual and holistically. The homeopathic medicines called remedies have been used generally for their placebo effect. The materialistic proof of the effect of low dose substances has brought the importance of homeopathic remedies by modulating the epigenome. The study of the pharmacological drugs in pharmacogenetics and pharmacogenomics should cover homeopathic remedies also or even as a specific field as homeo genetics and hemogenomics.

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