

# Personalized Medicine Toward Multiple Sclerosis; Current Challenges and Future Prospects

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Received November 20, 2016

Accepted February 18, 2017

Published online February 26, 2017



## Please cite this article

as follows: Javan MR, Jalali Nezhad A, Safa A, Mohammadi MH, Jamebozorgi K. Personalized medicine toward multiple sclerosis; current challenges and future prospects. Int J Basic Sci Med. 2017;2(1):11-15. doi:10.15171/ijbsm.2017.03.



## Abstract

Multiple sclerosis (MS) has not been comprehensively characterized in the 21st century yet. MS is an autoimmune neurodegenerative disease of the central nervous system (CNS) with unknown etiology. It is a heterogeneous disease both in the course and clinical symptoms and in the clinical response to treatment. Pharmacogenomics has potential to impress the treatment strategies of the diseases. It is related to the targeted populations that are genetically identifiable with the therapeutic interventions and it permits to elicit quick and optimized curative outcomes alongside the least possible side effects. In the case of successful manipulation of the personalized medicine, the trial-and-error approach for the treatment of diseases such as MS would no longer be mandatory. Moreover, pharmacogenetic and pharmacogenomic investigations contribute to the determination of genetic background of individual patients and may open new horizons to the personalized medicine. By identifying the various biological and social determinants of MS outcomes, personalized medicine could be applied in medical interventions and psychosocial manifestations, exercise and nutrition. Application of this highly personalized approach is promising and hopefully would culminate in cost-effective care.

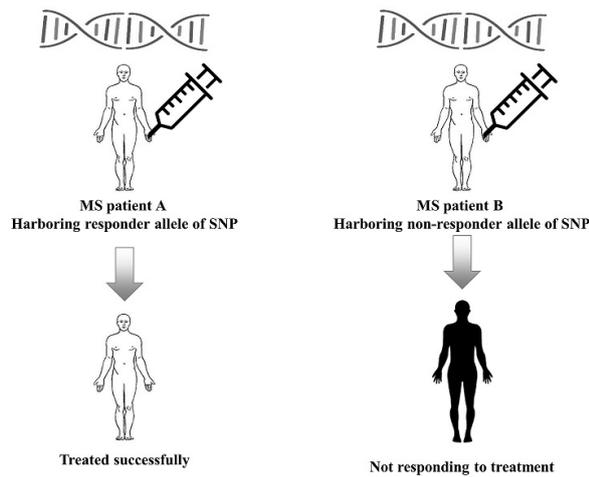
**Keywords:** Multiple sclerosis, Personalized medicine, Pharmacogenetics.

## Introduction

Pharmacogenomics is defined as the survey and application of the individual patients' specific genetic background to predict the quality and quantity of response to drug treatment. Although the human genomes are largely identical, small variations in the nucleotides of the genetic materials determine discriminations among individuals.<sup>1</sup> Variations of a single nucleotide in genome, which are known as single nucleotide polymorphisms (SNPs), are mainly found in the intergenic areas, resulting in insignificant differences in the final outcome. However, SNPs occasionally are responsible for the altered gene expression, culminating in aberrations in gene function. Clinical studies have established that SNPs impress the pharmacological responses toward drug administrations as well as metabolism rate of some drugs.<sup>2,3</sup> Using DNA samples obtained from mouth swab or venous

blood, by straight-forward and non-invasive methods, a certain disease-associated SNP position can be genotyped and subsequently the response to drug can be determined. This manipulation may allow the physicians to choose the best option to achieve the optimized results. Consequently, patients would receive the most effective therapy, side effects would be diminished and the overall cost of treatment would be reduced because of fewer drug trials (Figure 1).<sup>4</sup>

On the other hand, the aims of personalized medicine regarding the development of treatment and therapeutic procedures are best favored for each individual patient. Personalized medicine consists of both genetic and environmental factors in order to achieve new biotechnological tools and improve our understanding of disease etiopathology and patients management.<sup>5</sup> Advances in the genomic and proteomic



**Figure 1.** Schematic Diagram Demonstrating the Impression of Presence of an SNP in the Genome on the Status of Treatment Response in the MS Patients. MS patient A, whose genome harbors a responsive allele of a specific SNP, shows successful response to treatment. However, MS patient B fails to respond to therapy for carrying a non-responsive allele of the SNP.

techniques play a role in the development of personalized medicine manipulations.

So far, personalization implementation has been mostly dependent on the pharmacogenomics and pharmacogenetics, however other developments like identification of novel biomarkers have been conducted. Progresses in the Human Genome Project and cutting-edge efforts, like the ENCODE (Encyclopedia of DNA Elements) project,<sup>6</sup> have also contributed to and shed light on the novel approaches toward the development of personalized medicine.

This review aims to provide an overview of some new developments in the pharmacogenomics of MS as well as an outlook on the new approaches in the development of the personalized medicine.

### Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory chronic autoimmune disorder of the central nervous system (CNS) with the main specification of demyelination of neurons, resulting from aberrant activation of helper T lymphocytes. During demyelination progress, patients manifest impairment of the CNS function as well as mobility. In the magnetic resonance imaging (MRI), an evidence of the neuronal scarring or sclerosis is observed, which occurs as appearance of plaques.

Studies have attributed a role for CD8+ T cells in the pathogenesis of MS. CD8+ T cell clones specific for myelin antigens are isolated from the peripheral tissues of MS patients and normal individuals.<sup>7,8</sup> On the other side, major histocompatibility complex (MHC) class I genes are in linkage disequilibrium with the MHC class II genes associated with susceptibility to MS.<sup>9</sup> MHC class I-restricted myelin basic protein (MBP) is commonly presented by oligodendrocytes and cross-presented by Tip-dendritic cells (DCs) during experimental autoimmune encephalo-

myelitis (EAE), an animal model of MS.<sup>10</sup> Studies have revealed that Tip-DCs have the potential to activate the naive and effector CD8+ T cells against MBP expressing cells, contributing to the pathogenesis of MS.<sup>10</sup>

There are good reasons to target MS with the therapeutic strategies through the pharmacogenomics. Patients with the relapsing form of MS may currently be candidate for the treatment with the disease-modifying therapies (DMTs); however, many patients may not respond favorably to the selected treatment. DMTs are not considered as the absolute cure for MS, while they ameliorate the quality and quantity of relapses courses. Studies demonstrate that approximately half of the patients encounter response failure when treated with the first-line options like interferon- $\beta$  (IFN- $\beta$ ) and glatiramer acetate.<sup>11,12</sup> These patients are primarily subjected to the interventions and non-respondents are not subjected to the first-line therapeutics; hence, the patients may take early alternative DMTs during the disease course.

### Pharmacogenomic Investigational Strategies

There are two strategies to evaluate how SNPs influence the treatment response. The first approach, which is called candidate gene association studies (CGAS), emphasizes the exploration of selected few genes at a time and, therefore, facilitated and expedited identification. The first lane of CGAS starts with recognizing the pertinent proteins, which have already been associated with the biological mechanism of the disease or drug. Afterwards, the corresponding genes expressing those proteins are surveyed for the genetic variations.<sup>13</sup>

In the second method, genome-wide association studies (GWAS) are applied to compare each individual's DNA to a set of thousands of already identified SNPs throughout the genome. This method can be performed using the DNA microarrays which utilize SNP probes. By comparison of SNPs between respondents and non-respondents, it is possible to determine if significant differences occur between 2 groups. Beyond that, these studies provide the possibility to find other SNPs in genes, which have not already been detected to play a role in the disease, and to suggest new insights into the treatment mechanisms.<sup>14</sup>

### Interferon- $\beta$

Although Interferon- $\beta$  (IFN- $\beta$ ) has been vastly investigated in the pharmacogenomics of MS, other agents such as glatiramer acetate, alemtuzumab, natalizumab, fingolimod, mitoxantrone, teriflunomide, and dimethyl fumarate have also been studied.<sup>15,16</sup> A bulk of studies have assessed the possible link between the genetic variation and the status of IFN- $\beta$  response using different genotyping techniques. Although some studies in small groups of populations and tested SNPs have demonstrated the involvement of several individual SNPs in the response to IFN- $\beta$  therapy, GWAS by evaluating the profile of myriads of SNPs have suggested that the response circumstances are determined by several genes. Additionally, it was observed that most of these SNPs were harbored by genes

encoding glutamate and  $\gamma$ -aminobutyric acid (GABA) receptors, which play roles in regulating the neuronal excitation.<sup>17,18</sup> Considering the hypothesis that excessive excitatory activity of neurons plays a role in the pathogenesis of MS, these data shed new light on MS etiology and pharmacogenomics.

Besides GWAS introduction of multiple SNPs, it is essential to perform independent replication of the GWAS findings to achieve a valid and reliable conclusion for clinical application. Two SNPs have thus far been independently replicated, providing the most reliable stimulators of the response quality. In a GWAS, an SNP in the glypican 5 (*GPC5*) gene was found and subsequently was further evaluated in a follow-up experiment to confirm it.<sup>17,19</sup> The glypican 5 protein is involved in the cell signaling pathways and cell growth in the extracellular matrix.<sup>20</sup> This protein is expressed in MS plaques, and is thought to play an important role in MS pathogenesis, as polymorphism in *GPC5* gene was associated with MS proneness.<sup>21</sup> Another independently replicated gene variation was assessed indicating that SNP located in the interferon regulatory factor 5 (*IRF5*) gene plays a role in the IFN- $\beta$  response. *IRF5* is a transcription factor, which is involved in the regulation of target genes in the downstream of IFN- $\beta$ .<sup>22</sup> In a study, it was found that a certain SNP in the *IRF5* gene was associated with the non-response status to IFN- $\beta$  considering the drug bioavailability, MRI and duration of the first relapse outcomes.<sup>23</sup> Conversely, another study observed the opposite results, in which the same SNP in *IRF5* gene showed reverse trend, based on the relapse and long-term progression indices.<sup>24</sup> Given the above observations, it is only possible to conclude that the SNP in *IRF5* gene is likely involved in IFN- $\beta$  response and that further studies are necessary to determine if it is of any value to be applied in daily clinical practice.

Another factor that should be noted in the quality of response to IFN- $\beta$  therapy is to evaluate the impression of SNPs in promoting neutralizing antibodies (NAbs) against IFN- $\beta$ .<sup>25</sup> IFN- $\beta$  with protein structure has the potential to induce the immune responses to develop NAbs and neutralize its function. This kind of observation has occurred in IFN- $\beta$ 's phase III pivotal trial, implicating a negative relation between the presence of NAbs and the status of clinical response to the drug.<sup>26,27</sup> Alternately, further evaluations indicated that NAbs impressed the bioavailability of IFN- $\beta$ , hence decreased the therapeutic function.<sup>28</sup> Moreover, several SNPs in human leukocyte antigen (HLA) genes have been found with the susceptibility of protection of development of NAbs responses.<sup>29,30</sup> Considering all the facts, it is still premature to achieve consensus about the limiting role of NAbs against IFN- $\beta$  therapy in clinics and, therefore, the evaluation of NAbs in practice is not yet completely applicable.

### Glatiramer Acetate

Glatiramer acetate (GA) is also the first-line DMT that is prescribed for relapsing types of MS,<sup>31</sup> and as compared with IFN- $\beta$ , less pharmacogenomic trials have evaluat-

ed the GA response around the personalized medicine, with promising results underlying the effect of genetic variations for clinical testing. Auto-immune process is the main player in the demyelination of MS, and studies propose that GA binds to the MHC class II molecules, resulting in the impairment in the development of auto-immune responses.<sup>32</sup> Consequently, researchers have speculated the presence of important genetic variations in the HLA locus that may impress the quality of GA response in MS.<sup>33</sup>

While several genetic variants have been found in the HLA locus to be associated with the GA response in MS, there is uncertainty about the importance of HLA locus in the GA treatment response. Although studies have indicated that *DRB1\*1501* allele may be useful as a predictor of response status to GA therapy, some surveys have rejected its significance in replication trials.<sup>11,33-36</sup> The discrepancy between the observations may stem from the difference in the ethnicity of the studied population, sample size, respondent or non-respondent definition criteria, and protocol of the study. Moreover, this allele has also been shown as a significant predictor of susceptibility to MS.<sup>37</sup> On the other hand, some genetic variants in genes such as T cell receptor beta locus (*TRB*) and cathepsin S (*CTSS*) need replication studies for more validations; combinational impression of the genes, which encode inflammatory cytokines and cytokine receptors like *TGFB1\*G*, *DRB1\*15*, and *IFNARI\*G*, *CCR5\*d*; and finally HLA haplotypes including *DR17-DQ2* and *DR15-DQ6*.<sup>11,33-36</sup>

A retrospective cohort study analyzed several pharmacogenetic markers considering IFN- $\beta$  and GA, and proposed that individuals harboring combinations of SNPs including *CCR5\*d*, *TGFB1\*G*, *DRB1\*15*, and *IFNARI\*G* were more likely to respond to IFN- $\beta$  than to GA. Conversely, those that harbored a *CCR5\*w* allele or *CCR5\*w/w* genotype with *CTLA4\*G* allele were suspected to be IFN- $\beta$  non-respondent, hence GA therapy was privileged.<sup>38</sup> Further comparative clinical trials among the pharmacogenomics of the DMTs would be promising in contributing clinicians in selecting potentially relevant drugs for a particular individual.

### Natalizumab, Teriflunomide and Fingolimod

Natalizumab, fingolimod, alemtuzumab, and teriflunomide are currently used in MS treatment. However, no study has evaluated the role of pharmacogenomic marks in the assessment of response quality to these drugs. Further efforts may be required concerning these drugs as well as some newly upcoming drugs in order to validate them as the potentially beneficent agents for practical application.

### Personalized Epigenomic Prospects for Multiple Sclerosis

Studies demonstrate that autoimmune disorders have a remarkable epigenetic basis that can be attributed largely to the influence of the environmental contributing factors on the immune system.<sup>39</sup> Being armed with an un-

derstanding of the precise epigenetic modifications that occur in a patient's genome with an autoimmune disorder may be beneficial in guiding us in the knowledge of which gene may need to be regulated and through which epigenetic regulatory mechanisms.<sup>40</sup> Autoimmune diseases are often associated with the age of patients; and the increasing epigenetic divergence that occurs during the aging process demonstrates the important role of the personalized epigenetics in managing and monitoring of these kind of diseases under the impression of aging process. Nowadays, there is consensus that personalized epigenetics has the potential to revolutionize the approaches of diagnosis, prognosis, and management of autoimmune diseases, like MS.<sup>41</sup> The core of the personalized epigenetics is considered to be inter-individual variations in several epigenetic signatures, including DNA methylation, histone modifications, and microRNAs. Moreover, computational epigenetics has provided new opportunities to construct the complexities in the application of the epigenomic data and how it can be taken into practice in diagnosis, prognosis, and therapy of patients. In addition, the improving knowledge of the epigenetic biomarkers and personalized epigenetic responses toward drugs and environmental toxic agents would be the appropriate and cutting-edge tools to suit the use of the epigenetics in personalized epigenetic medicine.<sup>42</sup> It seems that the future of the personalized epigenetics is very bright and promising and there is no doubt that this area would develop outstandingly and ultimately revolutionize tools to be used in the clinical practice, especially in patients with autoimmune disorders.

### Conclusions

Incongruous and various types of responses have been observed in the MS patients receiving the DMTs. These patients need to be implemented with predictive examinations under the personalized medicine concepts to orientate them toward more efficient treatments. Along with advances in the drug discovery, it is favorable to choose a therapy concerning the unique genetic background of an individual. Hence, identification of genetic markers affecting the response quality of current DMTs to MS can be considered as a promising start that has the potential to culminate with further identifications in the future. On the other side, epigenetics and pharmacoeigenetics have opened new bright horizons toward the personalized medicine, especially for diseases with the epigenetic basis in their etiopathogenesis like MS. Currently, it is totally believed that pharmacogenomics and pharmacoeigenetics have the potential to be applied in the MS therapy and improve the therapeutic profile of the MS patients considering the cost of the treatment, efficacy of the drug agent, and duration of the patients' improvement.

### Ethical Approval

Not applicable.

### Competing Interests

Authors declare that they have no competing interests.

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