

Pharmacogenomics in multiple sclerosis: getting the right medicine to the right patient

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Disease-modifying therapies in multiple sclerosis have demonstrated a beneficial effect on disease activity. Furthermore, an increasing number of new therapeutic strategies with a diverse set of actions are becoming available. However, not all patients respond to current disease-modifying therapies, and a substantial interindividual variability exists in both efficacy and toxicity. This inevitable and unprecedented resource of new therapies and the potential risk for treatment failure emphasizes the necessity of personalized therapy for patients with multiple sclerosis. Currently, there is a lack of markers that reliably correlate with responsiveness to disease-modifying therapies in multiple sclerosis. Pharmacogenomics holds great promise for individualized therapy and is a reality in several types of malignancies, in which markers influencing efficacy and toxicity of therapy are identified and used to make therapeutic decisions. Nevertheless, pharmacogenomics of multiple sclerosis is still in its infancy, and big efforts should first be made in order to identify markers for treatment efficacy that may help tailor drug therapy in patients with multiple sclerosis.

Multiple sclerosis (MS) is the most common cause of chronic neurological disability in young people. It is considered to be a T-cell-mediated autoimmune disease of the CNS, pathologically characterized by autoimmune inflammation, demyelination, axonal damage and gliosis. To date, the etiology of MS remains unknown; however, it is assumed that both a complex genetic background and environmental triggers, such as viral infections, contribute to disease manifestation (as reviewed by Sospedra and Martin [1]). Evidence of heterogeneity in MS is not only observed at the level of clinical manifestations (relapse-onset versus primary progressive forms), disease course (benign versus severe evolution), morphological alterations of the brain found by MRI (inflammation versus atrophy) [2,3], or composition of lesion pathology (cell-mediated versus antibody-mediated) [4], but also in the response to treatment [5,6]. Thus, two people with MS who take the same medication, for instance, may have very different clinical responses. One may continue to have relapses and progression of the disease in spite of treatment, while the other experiences few, if any, relapses and shows a lack of disease progression. Although the aspects underlying this heterogeneity are not completely understood, genetic factors are likely to play an important role. Moreover, given the complex nature of the disease, the heterogeneity observed in the response to treatment is probably explained by the contribution of multiple genes.

Evidence for the necessity of individualized therapy in multiple sclerosis

Disease-modifying therapies (DMTs), such as interferon- β (IFN- β) 1a, IFN- β 1b, glatiramer acetate (GA), mitoxantrone and natalizumab, are the mainstay of treatment in relapsing-remitting MS and have demonstrated a beneficial effect on disease activity, as measured by both clinical and MRI parameters [7-14].

Nevertheless, DMTs are partially effective, and their long-term impact on disease progression remains elusive. In addition, not all patients respond to current DMTs. For instance, the percentage of patients that will show a lack of response to IFN- β or GA is estimated at approximately 20-55% of treated patients, depending on the clinical and radiological criteria used to evaluate treatment failure [15,16]. While the percentage of nonresponders to mitoxantrone and natalizumab is expected to be much lower compared with IFN- β and GA, the risks of serious adverse reactions, such as cardiotoxicity, leukemia or progressive multifocal leukoencephalopathy, are nonetheless a major concern [17-19].

Unfortunately, criteria to classify patients into responders and nonresponders to DMTs are usually applied after 1 or 2 years of follow-up. Hence, many patients are treated with DMTs without ultimate benefit and at high socioeconomic cost. In addition, patients receiving ineffective therapy accumulate further disability

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and often suffer treatment-related side effects. It is, therefore, highly desirable to identify surrogate markers that allow early identification of treatment failure or, ideally, even predict nonresponder status. Although several markers have been proposed [20–25], to date, it is impossible to predict which patients will respond favorably to DMTs in MS.

The better understanding of disease immunopathogenesis has allowed the development of new treatments and substantially changed the scenario of MS treatment. Several new treatment trials investigating promising therapeutic strategies, such as the oral therapies fingolimod [26] and cladribine [27], or the monoclonal antibodies alemtuzumab [28], daclizumab [29] and rituximab [30], are currently under investigation, and emerging therapeutic targets continue to be explored. Furthermore, patients begin treatment earlier, and combinations of therapies are being studied in an attempt to improve existing therapies.

In the near future, with this unprecedented availability of newer therapies, the choice of a first-line agent will become more complicated, and risk:benefit ratios are likely to play a major role in this decision process.

The increasing number of new therapies for MS and the potential risk for treatment failure and/or serious adverse reactions make individualized drug therapy a high priority for MS. It will be important to administer treatment to those patients who are likely to respond to it.

Pharmacogenomics in multiple sclerosis: where does the field stand at present?

The field of pharmacogenomics has evolved over the past years from the analysis of single genes or proteins to current approaches broadly analyzing the entire genome or proteome. Pharmacogenomics involves the application of genome technologies such as gene-expression profiling, SNP screens and proteomics to predict patient response and toxicity to drugs, with the ultimate goal of facilitating the individualization of patient treatment (as reviewed by Wolf *et al.* [31]). Identification of subgroups of patients who differ in their response to treatment could help to identify the best available drug therapy according to the genetic profile.

Gene-expression profiling is the study of the response that multiple messenger RNA species present in a given tissue or cell type to specific conditions or treatments. At present, transcriptional profiling is possible through DNA microarrays. Although the emerging and promising

next-generation DNA sequencing technologies (as reviewed by Mardis [32]) also allow large-scale gene-expression profiling, available data on this field are still limited.

DNA microarrays consist of oligonucleotides or complementary DNA molecules of known composition attached to a surface in an ordered, predetermined fashion at extremely high density, as reviewed by Stoughton [33]. Microarray technology allows one to profile changes in the expression levels of thousands of genes simultaneously in one hybridization experiment. Current microarray platforms contain probes for nearly all human transcripts and have the potential to aid in individualized treatment design in MS by the identification of the genomic signatures that distinguish responders from nonresponders to a particular treatment. These signatures consist of a set of differentially expressed genes (up- and down-regulated) between the two conditions that may serve as clinical biomarkers for predictors of response to particular therapies in MS.

A significant body of data on gene-expression profiling has been generated in MS. Even though results are promising, many discrepancies are found when comparing results from different studies using similar methodology. It should be taken into account that microarray experiments are multistep processes, and many sources of variability, such as intraindividual and interindividual variations, the use of different sample collection techniques, the use of different criteria and statistical approaches to analyze data and differences in the experimental conditions, to name a few, may contribute to the discrepancies and high rates of false positives observed in these studies (as reviewed by Comabella and Martin [34]). The majority of MS treatment-related transcriptional profiling studies have been performed with the goal of understanding the transcriptional changes induced *in vitro* or *ex vivo* by IFN- β therapy. Only a few studies, based on small cohorts of patients and using different methodologies, investigated end points directly measuring drug response in treated patients [22,35–37]. Interestingly, these studies report the presence of transcriptional differences between IFN- β responders and nonresponders, observed for some of the cases even before initiation of treatment. However, it is important to mention that replication studies of candidate expressed genes in large cohorts of treated patients with long clinical and/or radiological follow-ups are needed before using these genes as markers to predict response to IFN- β in clinical practice.

Additional transcriptional profiling studies searching for molecular differences between responders and nonresponders to other DMTs or emerging therapies have not been reported in the literature.

Genetic polymorphisms are known to contribute in the individual responses to therapies, either by altering the pharmacokinetics and pharmacodynamics of drugs or by modifying the cellular response to treatments. Several genetic properties, such as prevalence in the genome and stability, to cite a few, make SNPs the ideal markers for many DNA-analysis applications, including pharmacogenetics. Pharmacogenetic studies aim to identify the allelic variants that influence response to drugs by comparing the allele frequencies obtained for each genetic polymorphism between responders and nonresponders to a specific treatment. These studies can be performed either at the candidate-gene level or at the genome-wide level by using different methods such as DNA microarrays, electrophoresis, mass spectrometry-based SNP assays and plate readers, among others.

The vast majority of pharmacogenetic studies in MS have been related with the response to IFN- β [38–44]. These studies genotyped polymorphisms located in genes that are part of the type I IFN pathway, such as the IFN receptors 1 and 2 (*IFNAR1* and *IFNAR2*), or genes known to be induced by IFN- β . In other studies, the influence in the response to IFN- β of HLA class II (*DRB1*, *DQA1* and *DQB1*) alleles or the *HLA-DR2* haplotype was analyzed. Overall, results from these studies revealed either lack of association or weak and unreplicated associations of candidate genes with the response to IFN- β .

To date, only one genome-wide pharmacogenomic study has been published in MS [45]. The study aimed to identify genes linked to the response to IFN- β and was performed on pooled DNA using SNP microarrays. While previously reported pharmacogenomic associations were not confirmed, the study identified interesting candidates, such as genes involved in neuronal repair and growth, and over-representation of genes related to ion channels and signal transduction pathways such as γ -aminobutyric or glutamate receptor genes. Similar genome-wide pharmacogenomic studies searching for genes associated with the response to other MS therapies have not yet been published.

The influence of allelic variants in the response to GA has remained far less explored, and is restricted to only two studies. In the first study [20], the *HLA-DRB1*1501* allele was

reported to be associated with GA efficacy. In a more recent study [25], 27 candidate genes were selected mostly based on their implication in MS pathogenesis and the mode of action of GA. Even though, in the latter study, attractive genes such as the T-cell receptor β (*TRB β*) and the Cathepsin S (*CTSS*) were proposed as candidates for GA response, the previous association found with the *HLA-DRB1*1501* could not be confirmed. Overall, the paucity of such data suggests the need for more GA-related pharmacogenetic studies. Despite discrepancies between HLA and response to treatment, the *HLA-DRB1*1501* allele is a validated marker of MS disease susceptibility and should be taken into account in the analysis of the response to treatment in MS to control for its potential confounding effect.

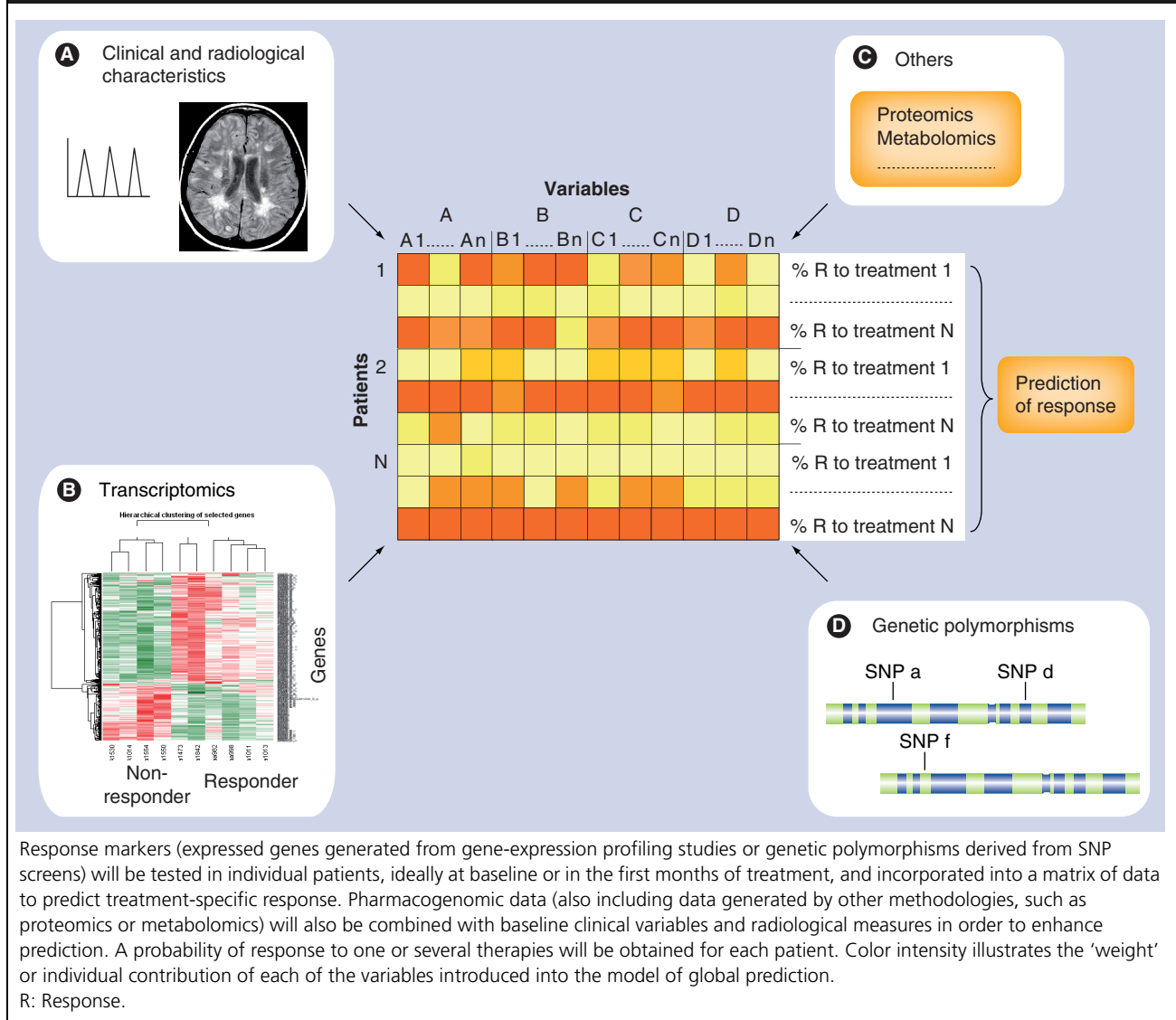
In general, data available from pharmacogenetic studies in MS reflect that the response to treatment is complex and polygenic in nature, and highlight the need for more studies.

Proteomics is the study of changes in part or all of the protein species present in a given tissue or cell type. Mass spectrometry-based approaches have gained significant interest for the analysis of complex protein mixtures. Advances both at the level of mass spectrometry hardware and data analysis software have expanded the applications of proteomics to include biomarker discovery. Thus, proteomics will allow the identification of differences in protein profiles between two biologically distinct conditions, that is, responders and nonresponders to a specific treatment. Although great progress has been made in proteomics over the last years, proteomics is still in its infancy. Proteomic studies in MS are scarce, and studies comparing differentially expressed proteins between responders and nonresponders to therapies by using this technology are not published as yet.

How pharmacogenomics will evolve in multiple sclerosis?

Ideally, markers (principally genetic polymorphisms, but also expressed genes) that are known from the pharmacogenomic studies to be of relevance in the response to the various MS therapies will be tested in patients before starting treatment or in the first months of therapy. Results from these markers (i.e., higher or lower expression levels for a gene or set of genes, allelic variations for selected genes) may be included in a multivariate analysis that will make predictions of the response of a particular MS patient to the existing spectrum of therapies (Figure 1).

Figure 1. Individualized therapy in multiple sclerosis to predict treatment efficacy by means of pharmacogenomics.



Response markers (expressed genes generated from gene-expression profiling studies or genetic polymorphisms derived from SNP screens) will be tested in individual patients, ideally at baseline or in the first months of treatment, and incorporated into a matrix of data to predict treatment-specific response. Pharmacogenomic data (also including data generated by other methodologies, such as proteomics or metabolomics) will also be combined with baseline clinical variables and radiological measures in order to enhance prediction. A probability of response to one or several therapies will be obtained for each patient. Color intensity illustrates the 'weight' or individual contribution of each of the variables introduced into the model of global prediction.

R: Response.

Additionally, changes in the expression levels of selected markers (mainly expressed genes) may be monitored in the initial stages of treatment administration to improve dosing and regimen optimization. Genes identified by pharmacogenomic approaches such as gene-expression profiling and/or SNP screens should also be combined with baseline clinical variables (i.e., number of relapses in the previous years, Expanded Disability Status Scale score and disease duration) and radiological measures (i.e., degree of inflammation and atrophy) in order to enhance prediction of therapeutic outcomes. Although still in their infancy, markers generated

by means of other methodologies, such as proteomics or metabolomics, may also be incorporated in the analysis. In this multivariate analysis, prediction of response may be made in terms of probability of response or lack of response to a particular treatment or treatments. Based on these probabilities, the question will remain for neurologists to decide the best treatment option for the patient, possibly taking into account factors such as cost and toxicity, among others. Related to the latter, pharmacogenomics can also be used to identify markers (presumably genetic polymorphisms) that predispose patients to severe adverse drug effects. If known, genetic

polymorphisms can also be incorporated in a predictive model to identify those patients who will have life-threatening adverse reactions.

Pharmacogenomics in multiple sclerosis: future perspective

Individualized therapy is a reality in several types of malignancies, such as breast, colorectal and lung cancer, in which specific gene polymorphisms in drug-metabolizing enzymes and drug transporters or molecular profiles influencing efficacy and toxicity of anticancer therapy are identified and used in the treatment decision process [46–49]. Moreover, the FDA has recently updated the labels of several drugs to incorporate information on pharmacogenetic testing and guide treatment [101]. Nonetheless, pharmacogenomics in MS is still far from this futuristic scenario in which personalized therapy can be offered to MS patients, and many challenges remain that need to be overcome.

First, efforts should be made to better define the clinical and radiological criteria of response and treatment failure to each MS therapy. For instance, in the case of IFN- β , the most widely prescribed DMT for MS, no consensus on the definition of lack of response to treatment has been reached yet. For personalized therapy, distinction between full and partial responses to a particular treatment may result in a more meaningful and practical classification. Given the current armamentarium of DMTs and the increasing number of new therapies that will soon become available for MS, identification of partial responders to a particular treatment seems sufficient reason to treat these patients with alternative therapies to which optimal response is guaranteed.

Second, there is a need for more therapeutic trials that incorporate large-scale pharmacogenomic

studies as part of their design. These studies will make possible the identification of reliable markers for treatment efficacy, and facilitate our capacity to individualize patient-specific treatment.

Although limited safety data are available, with the longer and more frequent use of new treatments, as well as with the combination of therapies, the potential risk for unexpected adverse reactions should be considered. Identification of the genetic polymorphisms associated with these adverse reactions will help to predict patients at high risk.

Finally, another issue that should be taken into account is that technologies used in pharmacogenomic studies are expensive. Nevertheless, individually tailored therapy will most likely avoid the ‘try and see’ prescribing and decrease the number of visits to the neurologist due to reduced frequency of adverse drug effects and increased probability of successful therapy. In the long term, all these factors together will probably give rise to a decline in the cost of healthcare.

In summary, evidence for the need for genomic-based personalized therapy exists in MS. The current armamentarium of DMTs and the increasing number of new therapies will complicate the selection of first-line agents to treat MS patients. The goal of pharmacogenomics is to maximize efficacy and minimize side effects of therapeutic agents. Although pharmacogenomics will be of help in the process of MS treatment individualization, further studies in large cohorts of patients incorporating pharmacogenomics are needed, in order to identify reliable markers that may be used to predict treatment efficacy and toxicity in individual patients by means of pharmacogenomic tests.

Executive summary

Evidence for the need of personalized therapy in multiple sclerosis

- Response to treatment is heterogeneous in multiple sclerosis (MS).
- Not all patients respond to current disease-modifying therapies (DMTs).
- There is a potential risk of serious adverse drug reactions.
- There is an increasing number of new therapies for MS.

Pharmacogenomics in multiple sclerosis: current status

- Available data in the field are still limited.
- Evidence suggests that the response to treatment in MS is complex and polygenic in nature.
- There is a current lack of markers that reliably correlate with responsiveness to DMTs.

Future directions of pharmacogenomic studies in multiple sclerosis

- There is a need for more therapeutic trials that incorporate pharmacogenomics as part of their design.
- Better definition of the clinical and radiological criteria of response and treatment failure to MS therapies is required.
- Efforts should be made to identify markers for treatment efficacy that may help tailor drug therapy in MS patients.

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