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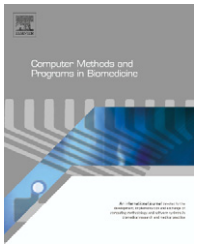

Artificial neural network prediction of clozapine response with combined pharmacogenetic and clinical data

Chao-Cheng Lin[a,b], *Ying-Chieh Wang*[c], *Jen-Yeu Chen*[c], *Ying-Jay Liou*[d], *Ya-Mei Bai*[d,e], *I-Ching Lai*[c], *Tzu-Ting Chen*[c], *Hung-Wen Chiu*[f,**,1], *Yu-Chuan Li*[g,*,1]

[a] *Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taiwan*
[b] *Department of Psychiatry, National Taiwan University Hospital and National Taiwan University College of Medicine, Taiwan*
[c] *Department of Psychiatry, Yu-Li Veterans Hospital, Taiwan*
[d] *Department of Psychiatry, Taipei Veterans General Hospital, Taiwan*
[e] *Department of Psychiatry, College of Medicine, National Yang-Ming University, Taipei, Taiwan*
[f] *Graduate Institute of Medical Informatics, Taipei Medical University, Taiwan*
[g] *Institute of Biomedical Informatics, National Yang-Ming University, Taiwan*

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ABSTRACT

Although one third to one half of refractory schizophrenic patients responds to clozapine, however, there are few evidences currently that could predict clozapine response before the use of the medication. The present study aimed to train and validate artificial neural networks (ANN), using clinical and pharmacogenetic data, to predict clozapine response in schizophrenic patients. Five pharmacogenetic variables and five clinical variables were collated from 93 schizophrenic patients taking clozapine, including 26 responders. ANN analysis was carried out by training the network with data from 75% of cases and subsequently testing with data from 25% of unseen cases to determine the optimal ANN architecture. Then the leave-one-out method was used to examine the generalization of the models. The optimal ANN architecture was found to be a standard feed-forward, fully-connected, back-propagation multilayer perceptron. The overall accuracy rate of ANN was 83.3%, which is higher than that of logistic regression (LR) (70.8%). By using the area under the receiver operating characteristics curve as a measure of performance, the ANN outperformed the LR (0.821 ± 0.054 versus 0.579 ± 0.068; $p < 0.001$). The ANN with only genetic variables outperformed the ANN with only clinical variables (0.805 ± 0.056 versus 0.647 ± 0.066; $p = 0.046$). The gene polymorphisms should play an important role in the prediction. Further validation of ANN analysis is likely to provide decision support for predicting individual response.

* *Corresponding author at*: No. 155, Section 2, Linong Street, Beitou District, Taipei 112, Taiwan. Tel.: +886 2 28267349; fax: +886 2 28202508.
** *Corresponding author at*: 250, Wusing Street, Sinyi District, Taipei 110, Taiwan. Tel.: +886 2 27361661x3347; fax: +886 2 27339049.
E-mail addresses: hwchiu@tmu.edu.tw (H.-W. Chiu), jack@tmu.edu.tw (Y.-C. Li).
[1] These authors contributed equally to this work.
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1. Introduction

Clozapine was the first atypical antipsychotic drug (also named second-generation antipychotics, SGA). Although more and more SGAs have been released into the market, clozapine is still regarded as the most effective antipsychotic for treating refractory schizophrenia [1,2]. A Cochrane review of comparative randomized trials concluded that clozapine is more effective than conventional antipsychotics for all patients with schizophrenia, and that the comparative advantage of clozapine is greater in patients whose condition is classified as treatment-resistant [3]. Clozapine has clinical response rates of 30–50% in treatment-refractory schizophrenia patients and it produces substantially fewer extrapyramidal side effects compared with conventional antipsychotic agents. As a result, it is often used for schizophrenic patients who respond poorly to conventional agents or are unable to tolerate side effects, such as extrapyramidal side effects. Despite such benefits, several adverse effects are often complained of, including sialorrhea, orthostasis, sedation, anticholinergic effects, weight gain, urinary incontinence and so on [4,5]. Moreover, the use of this antipsychotic carries significant morbidity from seizure and serious blood disorders such as potentially fatal agranulocytosis, the need for continual blood monitoring, and consequent high costs [6,7].

At present, there is little evidence to predict the clozapine response of an individual patient. Trial and error still remains the best option to find out which patient will benefit from clozapine. This has major implications both for successful treatment regimens and for the prevention of serious side effects. If we can predict the response to clozapine, we can make a better decision regarding the use of clozapine and reduce the number of unnecessary trials with ineffective medications. The pre-treatment identification of non-responders and the development of special treatment options is also an important task, for both efficacy and safety. In recent years, clinical and genetic studies have investigated this problem, but many of these studies have had inconsistent results that await unequivocal confirmation [8–22]. Although genetic variation may have a significant effect on clozapine response [23], there is no single factor that can predict it. It has been postulated that there are contributions from the combinations of mutations in neurotransmitter-receptor-related genes.

Multiple logistic regression (LR) is a widely used statistical modeling technique in which the probability of a dichotomous outcome event is assumed to be related to a set of explanatory variables in a sigmoid relationship. LR is a generalization of linear regression. The response (dependent) variable is the natural logarithm of the odds ratio representing the ratio between the probability that an event will occur and the probability that it will not occur (e.g., probability of being a responder or not) [24]. Arranz et al. [9] used LR analysis to predict clozapine response with combinations of 19 genetic polymorphisms. They found the combination of five polymorphisms in the serotonergic system (5-HT_{2A} 102 T/C and His452Tyr, 5-HT_{2C} −330-GT/−244-CT and Cys23Ser, 5-HTTLPR) and one in the histaminergic system (H2-1018-G/A) can successfully predict the response to clozapine in 76.8% of patients. The combination had a sensitivity of 95.89%, and a specificity of 38.3%. Therefore, predicting clinical outcome before treatment is possible by combining pertinent information from key genes [9].

While LR is a very powerful modeling tool for prediction, it assumes that the response variable (the log odds) is linear in the coefficients of the predictor variables [25]. However, the relationship between genetic polymorphisms and the log odds of clozapine response may be non-linear and complicated. In addition, the predictive models have to be tested with unseen data. The artificial neural network (ANN) is a form of artificial intelligence that employs non-linear mathematical models to mimic the human brain's own problem-solving process. Just as humans apply knowledge gained from past experience to new problems, a neural network takes previously solved examples to build a system of "neurons" that makes new decisions, classifications, and forecasts. The classification rules are not written into algorithms, but rather are learned by the network from examples. An ANN comprises layers of neurons.

The input layer is formed by neurons that may receive a single clinical or genetic feature for a specified problem. The hidden layer of neurons receives the data from the input layer, and is connected to the output layer, with multiple connections between neurons among the layers by weights. The hidden layers process the information and feed the response to an output layer. The output layer forms the outputs of the network. The input–output relationship is controlled by a transfer function in the hidden layer of neurons, thus allowing the network response to be non-linear. During the supervised training stage, a dataset is presented to the ANN with the correct outputs available. The ANN is trained by first randomly initializing the connection weights between the neurons and then running the data through the network and comparing the output with the known responses. The process repeats and the network alters the weights between connections so that the errors in the outputs are reduced to negligible values. The ANN can then be used for prediction. Unlike logistic regression, which fits the data to a descriptive function, in ANN the input data is transformed on each layer, changing its dimensional space to define the rule to get to the decision region. Thus the two approaches are inherently different, raising the question of whether one approach has a better predictive performance than the other.

To our knowledge, there do not appear to be any published papers to date regarding the prediction of clozapine response by means of ANNs. To investigate this problem, we applied ANNs and LR to the analysis of both clinical and pharmacogenetic data from schizophrenic patients taking clozapine in an attempt to achieve accurate predictions of clozapine response for unseen individual patients. A comparison of the performance between the models was made. Second, we compared the performance of ANN analysis with genetic variables and that with clinical variables.

2. Methods

2.1. *Study population*

Our sample consisted of 93 inpatients in Yuli Veterans Hospital in Taiwan. Some of the participants were included in our