

Genetic markers anticipate response to citalopram in a majority of patients

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Objective Scientists have concluded that genetic profiles cannot predict a large percentage of variation in response to citalopram, a common antidepressant. Using the same data, we examined if a different conclusion can be arrived at when the results are personalized to fit specific patients.

Methods We used data available through the Sequenced Treatment Alternatives to Relieve Depression database. We created three boosted Classification and Regression Trees to identify 16 subgroups of patients, among whom anticipation of positive or negative response to citalopram was significantly different from 0.5 ($P \leq 0.1$).

Results In a 10-fold cross-validation, this ensemble of trees made no predictions in 33% of cases. In the remaining 67% of cases, it accurately classified response to citalopram in 78% of cases.

Conclusion For the majority of the patients, genetic markers can be used to guide selection of citalopram. The rules identified in this study can help personalize

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Introduction

It is generally assumed that the discovery of genetic processes and markers should precede translation to practice. This is not always the case. It is theoretically possible that scientists may find no markers or genetic processes that are relevant in the general population but when the findings are restricted to specific patients, as when the data are personalized, the findings may be radically different. In short, recommendations to one patient may differ from advice to the average patient. This possibility changes how scientific findings should be approached in practice setting. Translational research requires us to pay less attention to conclusions of the scientist and more attention to the data collected by the scientist. In particular, it requires us to reanalyze the subset of scientist's data that is relevant to the patient at hand. To demonstrate this possibility, we set out to reexamine scientific data on response to antidepressants and to see if personalized recommendations could differ from the general scientific findings.

The search for genetic markers for response to antidepressants has identified a number of markers. Variants in HTR2A, GRIK4, KCNK2, FKBP5, PDE11A and BDNF, and SLC6A4 have been identified in some but not all studies to be predictive of response to anti-

depressants (Peters *et al.*, 2004; Cabanero *et al.*, 2009; Laje *et al.*, 2009; Paddock *et al.*, 2007).

Despite progress, the effect size is small and the percentage of outcomes correctly predicted from any single genetic marker is near random chance (Garriock *et al.*, 2010). This has led the investigators to conclude that there is 'limited clinical utility in matching antidepressants to patient's genetic profile' (Peters *et al.*, 2008). The studies to date have not examined the combination of various genetic markers or examined subgroups of patients among whom response might be predicted more accurately. In this study, we will examine the ability to predict response to citalopram from a combination of genetic markers within subgroups of patients.

Citalopram (brand names Celexa, Cipramil, etc.) is a common antidepressant prescribed in United States and many other markets (Willetts *et al.*, 1999). Worldwide, more than 18 million patients have taken this medication but the majority of patients (60%) do not achieve remission of their depression symptoms (Heath, 2007; Fava, 2009). Untreated or poorly treated depression leads to significant functional impairment and may even lead to self-medication through alcohol and illicit drugs and

sometimes suicide. Poorly responsive or untreated patients are twice as likely to be hospitalized and incur 19 times greater cost than patients with effectively treated (Crown *et al.*, 2002). One way out of these grim statistics is to anticipate response to citalopram and prescribe it for patients who are likely to benefit from it. As it may take weeks to determine if an antidepressant will be helpful, it would be useful to know in advance if a particular medication is likely to be successful for a given patient.

Data suggest that response to antidepressants depends on a host of factors including age (Zisook *et al.*, 2007), comorbidities such as diabetes (Bryan *et al.*, 2009), sex (Young *et al.*, 2009), subtype of depression, for example anxious depression (Fava *et al.*, 2008), or maternal depression (Weissman *et al.*, 2006), as well as other factors. The wide variation in phenotypic predictors of response to antidepressants suggests genetic factors might be affecting the outcomes of different subgroups. Of particular interest are studies of differences among sex and race in response to antidepressants (Lesser *et al.*, 2007). For example, Peters *et al.* (2008) found that seven variants of polymorphisms in the CYP2D6, CYP2C19, CYP3A4, CYP3A5, and ABCB1 genes were associated with citalopram metabolism. Six of the seven variants were found in African-Americans and not in Caucasians. These data support the notion that there are different markers for response to treatment in different subgroups of patients.

Subgroup analysis is not new and many studies examine response to antidepressants among different groups. Looking at racial subgroups is one way to do so. One can also group patients by age, by comorbidity, depression subtype or clinical features, and by a host of different factors including genetic markers. In fact, any one of the genetic markers in a patient profile can be used to define a new subgroup. If there are 'n' predictors of response to therapy, there are 2^n possible subgroups. This raises the possibility of a very large number of subgroups, too many to be practical. Not surprisingly, none of the studies reported to date have implemented a complete subgroup analysis. One way to limit the number of subgroups examined is to examine only those groups within which an accurate prediction can be made. To accomplish this, we used Classification and Regression Trees (CART) as implemented in the SPSS 17 Tree add-on package (IBM North America, New York, New York, USA).

CART is used to group cases. When a new patient presents, the group corresponding to the patient is identified and used to guide the patient. This approach is similar to an earlier proposal by Alemi *et al.* (2009) in which cases in the database are ordered in the sequence of their similarity to the patient and the sequential probability ratio test is used on the next case until

response to treatment is statistically significant. In both approaches the advice to the patient is based on the outcomes of similar cases within the database. Both approaches are part of algorithms called by statisticians as 'local analysis' (Cleveland, 1979; Cleveland and Devlin, 1988; Hastie and Tibshirani, 1996), and that we call 'patients-like-me algorithms'. These approaches allow one to select a small subset of data and anticipate a patient's response from the experience of cases within that subset. Contrary to usual statistical procedures, the objective is not to rely on a large data set but on the smallest most relevant subset of data.

Methods

This study examines the response to citalopram through a reanalysis of the data available from National Institute of Mental Health: the Sequenced Treatment Alternatives to Relieve Depression database. National Institute of Mental Health provided a public release of the STAR*D database in August 2008. The design of the STAR*D study has been described elsewhere (Fava *et al.*, 2003). The STAR*D project enrolled more than 4200 outpatients (aged 18–75 years) diagnosed with nonpsychotic major depressive disorder. Data were collected from 41 primary care and mental health clinics. All of these patients were prescribed citalopram. If patients did not achieve remission or could not tolerate the medication, they were encouraged to proceed to the next random assignment, in which they received other medications or cognitive therapy. Those who achieved remission or reduction in symptoms and tolerated acute treatment were followed for 12 months.

Genetic profiles were available on 1933 cases within the STAR*D database. The DNA sampling and the definition of remission have been described in a previous publication (Peters *et al.*, 2008). In brief, patients were considered responsive to treatment if at follow-up they were in remission; defined as patients scoring 5 or less on the Quick Inventory of Depressive Symptomatology (Clinician Rating) at follow-up. Genotyping was conducted on two platforms: Affymetrix Human Mapping 500 K Array Set and the Affymetrix Genome-Wide Human SNP Array 5.0 (SeqWright Inc., Houston, Texas, USA). This resulted in 430 198 validated single nucleotide polymorphisms (SNPs) for each case. Garriock *et al.* (2010) identified the top 25 SNPs associated with response to citalopram in a genome-wide association study. We focused on these 25 markers because they were the most likely SNPs that might affect response.

The classification of cases within the STAR*D database into different subgroups was done using a variation of the CART procedure. A traditional CART classifies cases within the data set by progressively splitting the data into two additional classes (two child nodes) so that the new

classes can explain the most variance of the response to citalopram. In particular, at every step, the CART procedure used the Gini index (quadratic entropy), to select one of the 25 SNPs to classify the cases within the database. The procedure continued until all cases were classified into subgroups of at least 10 cases. The traditional CART procedure leads to a classification tree. Each node along a branch in the tree describes the presence of a specific genetic marker. The entire branch describes a particular genetic profile. The final node in the branch shows the subgroup of patients with the same genetic profile and, as far as possible, homogenous response to citalopram. For example, the right hand branch of the tree in Fig. 1 describes the situation in which rs7239368 is AG or AA. A total of 482 patients fall into this branch, and 84.4% of these patients respond negatively to citalopram. Therefore, if the patient-at-hand has the genetic profile that matches this group, then there is a good chance that this patient will also respond negatively to citalopram.

Since 1990, several investigators have shown methods for boosting the accuracy of CART (Schapire, 1990; Freund and Schapire, 1996; Friedman *et al.*, 2000; Friedman, 2001). In boosted trees, the analyst selects misclassified cases and fits a separate tree to these cases. The procedure is repeated hundreds of times and the weighted average of the ensemble of trees is used to make the final predictions. Several studies have shown that boosted trees are more accurate than other classification systems such as logistic regression or trees without boosting; but boosted trees are difficult to interpret (Neumann *et al.*, 2004). We developed a variant of boosted trees, in which the branches of the tree lead to

subgroups in which the probability of positive or negative response to citalopram is significantly different from 0.5 ($P \leq 0.10$). This approach does not classify all cases, but the cases it does classify fall into categories in which the probability of response is significantly different from 0.5. The algorithm we used was as follows:

- (1) Fit a CART (10-fold cross-validation and pruning factor of 1) to all unclassified cases and identify the subgroups classified by each branch in the tree.
- (2) Stop if none of the subgroups identified have a probability of positive or negative response significantly different from 0.5 ($P \leq 0.10$).
- (3) Rename cases within subgroups with probability of positive or negative response not significantly different from 0.5 ($P > 0.10$) to 'Unclassified cases'. Specify exclusion rules by using the branches that defined the subgroups that were renamed.
- (4) Apply CART (10-fold cross-validation and pruning factor of 1) to cases not excluded in the previous step. This results in a new tree. The branches within this tree specify the inclusion rules.
- (5) Go to step one.

This procedure leads to an ensemble of trees. Each tree classifies the response of a particular set of cases. The last tree contains cases from subgroups, in which none meet the significance criterion. This procedure improves the performance of the initial tree similar to other boosting methods. Unlike other boosting procedures, it has the advantage that it stops after a few iterations and is easily interpretable as every branch within each of the ensemble of trees provides a rule for defining a specific subgroup of cases. Additional detail on our method of boosting the performance of CART is made available by the first two researchers.

The CART procedure was applied with 10-fold cross-validation and pruning, therefore, the percentage of cases correctly classified was unlikely to be due to over-fitting. The results we present are data on the accuracy of the cross-validated trees.

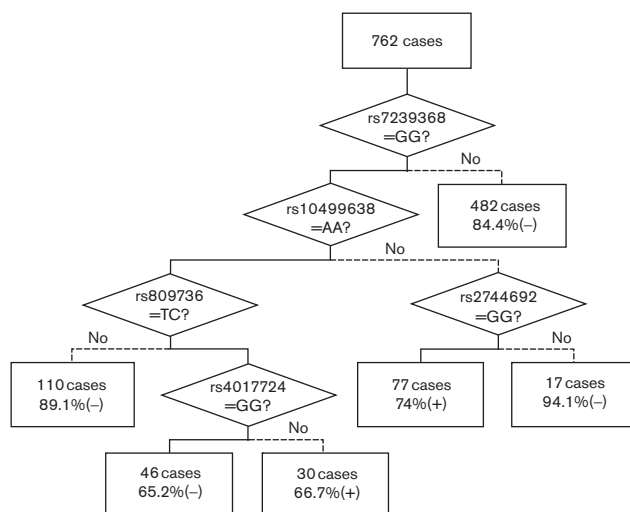
Results

The initial CART (without boosting) yielded a tree that correctly classified 56% of cases (standard error in risk 0.01). A lasso-penalized logistic regression with 10-fold cross-validation and 50 indicator variables was assessed. Two indicator variables represented the three possible genotypes of each one of 25 SNPs. At the optimal tuning parameter λ of 0.97, there were 47 nonzero indicator variables in the model:

$$\text{Probability of success} = \frac{1}{1 + e^{-z}}$$

Where:

Fig. 1



Classification of response to citalopram for 762 cases.

Z: -0.39	-0.12 (A2187317=AG)	-0.39 (A2187317=AA)	-0.01 (A1951600=TT)
-0.28 (A1951600=AA)	-0.95 (A4198575=AG)	-0.32 (A4198575=GG)	-0.31 (A2187089=AG)
-0.42 (A2187089=GG)	-0.34 (A2269443TC)	-0.19 (A2269443=TT)	-0.25 (A2260830=GG)
+0.15 (A2260830=AA)	+0.41 (A1897143=TC)	-0.25 (A1888385=AC)	-0.78 (A1888385=CC)
-0.02 (A4228427=GG)	+0.40 (A4228427=CC)	+0.04 (A2068542=AG)	+0.44 (A2068542=AA)
+0.75 (A1990776=AT)	+0.34 (A4218787=AG)	+0.51 (A4218787=GG)	-0.26 (A2165215=TC)
-0.17 (A2165215=CC)	+0.26 (A1996954=TC)	+0.13 (A1996954=TT)	-0.47 (A1809840=AG)
-0.23 (A2024840=AG)	-0.31 (A2024840=AA)	+0.29 (A2170173=TC)	+0.24 (A2170173=CC)
+0.21 (A1901209=GG)	+0.03 (A1901209=AA)	+0.36 (A1866894=GG)	-0.05 (A1866894=AA)
-0.10 (A2007509=CC)	+0.35 (A2007509=TT)	+0.22 (A2235053=GG)	-0.24 (A2235053=TT)
-0.22 (A2312802=AC)	-0.82 (A2312802=CC)	+0.25 (A4215770=CC)	-0.34 (A4215770=GG)
+0.17 (A2257126=TG)	-0.29 (A2257126=TT)	+0.35 (A1819122=TC)	-0.81 (A1819122=CC)

In the above regression, if the patient's SNP has the indicated allele, then it has a score of 1, otherwise 0. The regression correctly classified 66% of cases (Table 1).

One could accurately classify 61% of cases by merely predicting no one would benefit from citalopram. Therefore, the initial performance of CART or logistic regression was not adequate; we used our boosting procedure to identify subsets of patients for whom we could more accurately anticipate response to citalopram. The initial tree provided 71 subgroups of patients (branches in the tree), each with a different probability of positive response to citalopram. We excluded subgroups of patients, in which the probability of positive or negative response was not significantly different from random tossup. We then repeated our CART analysis for these more homogenous subgroups, as per algorithm provided earlier.

The boosted CART procedure created an ensemble of three related trees. There were 1933 cases (see Table 2). The first boosted tree was organized for 762 cases and accurately classified 81% of these cases in cross-validation. In step two, a tree was organized for 351 cases and accurately classified 74% of these cases in cross-validation. In step three, a tree was organized that accurately classified 76% of 176 cases. This algorithm left 644 (33%) of cases as unclassified; on these cases the algorithm made no predictions.

Table 1 Accuracy of logistic regression

Observed response	Logistic regression		
	Success	Failure	Total
Success	324	209	533
Failure	439	961	1400
Total	763	1170	1933

The corresponding author of this paper can provide 91 rules, combinations of SNPs, that identified which one of the trees were appropriate. These rules were derived from branches we excluded from the analysis and we refer to them as exclusion rules. In cases in which none of the three trees are appropriate, we cannot make a prediction. Once a tree has been selected, then each branch within the tree identifies a unique subgroup of patients. We refer to these rules as the inclusion rules. There were 16 inclusion rules (see Table 3). These rules can be used to further classify the patient into relevant subgroups. Once a patient has been classified into a relevant subgroup, then the average response of the group can be used to anticipate the outcome for the patient.

Table 3 identifies 16 inclusion rules identifying subgroups with different probability of positive response to citalopram, ranging from 84 to 6% (94% probability of negative response). The number of cases that fall within each subgroup is different, ranging from 13 to 482 cases. A patient may have more confidence in the advice of the system when they fall in the larger groups or if they fall in a subgroup with more extreme probability of positive/negative response. A statistical test can be done for the individual patient to see if the probability of positive response within their subgroup is significantly different from a particular value, say 0.5. Such a test provides guidance only to the patient that falls within the subgroup.

The overall accuracy of the ensemble of the three trees is the sum of the accuracy of each one, weighted by the percentage of cases classified by the trees. Therefore, the ensemble as a whole makes no predictions on 644 (33%) of cases and correctly classifies 78% of the remaining 1289 (67%) of cases.

Table 2 Anticipating response to citalopram using three trees no predictions were made in 644 (33%) cases

Observed response	First tree			Second tree			Third tree		
	Success	Failure	Total	Success	Failure	Total	Success	Failure	Total
Success	551	30	581	110	57	167	75	26	101
Failure	104	77	181	25	159	184	15	60	75
Total	655	107	762	135	216	351	90	86	176

Table 3 Inclusion rules for defining subgroups within the three trees

Tree	Node	rs2744692	rs2697992	rs4017724	rs6817919	rs10499638	rs809736	rs7239368	rs6046805	rs6127921	rs11701162	Anticipated response	Percentage	N
T1	2							AG AA				F	84	482
T1	5					AA	TT CC	GG				F	89	110
T1	7	GG				AC CC		GG				S	74	77
T1	8	AG AA				AC CC		GG				F	94	17
T1	9			GG		AA	TC	GG				F	65	46
T1	10			AG AA		AA	TC	GG				S	67	30
T2	4		GG CC						TT			S	84	62
T2	7		CG					TT			TG	S	77	13
T2	8		CG					TT			TT GG	F	79	14
T2	9		GG				TTTC	TC CC TC CC				F	90	81
T2	10		GG				CC	CC				S	69	13
T2	11		CG CC					TC	AA			S	69	128
T2	12		CG CC					TC CC	AC CC			F	65	40
T3	1				TT							F	86	76
T3	3				TC			AA				F	71	14
T3	4				TC			AG GG				S	70	86

Discussion

The purpose of this study was to identify groups of patients, on the basis of combinations of marker alleles, explaining the variance in citalopram response. The study provided 91 exclusion and 16 inclusion rules for anticipating response to citalopram. It may be helpful to provide an example of how these 107 rules can be used in a clinical setting. First, one obtains the patient's genetic profile, using the 25 SNPs identified in this study. Second, the exclusion rules are applied to determine which one of the three trees is appropriate. Third, the inclusion rules are applied to see which branch of the selected tree describes the patient. If a branch is identified, then the number of cases within the branch and the statistical significance of the finding are reported to the clinician/patient. For example, if a patient has allele AG for rs11128623, TC for rs6817919, and GG for rs7239368, then this patient is excluded from the first tree. If this patient has allele GG for rs2697992 and allele TT for rs6817919, then this patient is classified by the second tree. According to this subgroup, there are 62 cases that have the same pattern of alleles; citalopram reduced depression symptoms in 82% of these cases. Therefore, the evidence from the cases in STAR*D suggests that the patient-at-hand should try citalopram. Clearly, no patient or clinician can be expected to go through the rules by themselves. A computer program can facilitate the interpretation of the patient's genetic profile. These reports can improve in accuracy by including not only the patient's genetic profile but also the evidence-based implication of the profile for selection of appropriate medication.

Our analysis showed that for two thirds of patients, the majority of cases, we can accurately classify their response to citalopram. The unaided clinician's prescription of citalopram was effective in only 39% of cases. If a clinician would have followed our algorithm, the accuracy of his prescription would have nearly doubled to 78% of cases. Similar to the study by Garriock *et al.* (2010) there was a statistically significant relationship between the genetic profiles and observed response to citalopram. Unlike their study, the effect size was large and therefore, clinically more relevant.

Our findings were based on retrospective data analysis and the results that can be obtained prospectively in a new clinic could be very different. Before these findings can be used, we encourage prospective, double-blind randomized studies to test whether the 107 rules we have identified can improve anticipating response to antidepressants.

It is difficult to relate the 107 rules identified in this study to any specific biological process, and this was not the intent of our analysis. Nevertheless, a few speculations can be made. The existence of so many rules suggests that there may be multiple pathophysiological processes that lead to depression. Depression is not only clinically, but also likely genetically heterogeneous. It may be possible that the rules identified in the study correspond to etiological subtypes of depression.

Among the combinations of alleles at different genes comprising the subgroups in Table 1, we observed two

notable ones. These were characterized by the prediction of either success or failure in relatively large groups of patients, as well as a possibility of biological interaction, in addition to their observed statistical interaction. Of the three markers, identifying 110 cases with an 89% chance of nonresponse listed above, rs7238368 and rs809736 occur in the genes nucleolar protein 4 (NOL4), and RAR-related orphan receptor A isoform A (RORA), respectively, whereas rs10499638 is intergenic. NOL4 is highly expressed in both brain and testis. Its function is poorly understood. Nucleoli are the sites of ribosome-subunit production, although they are increasingly thought to have a variety of other functions. Furthermore, nucleolar dysfunction may be related to disease etiology, including in neuropsychiatric conditions such as Alzheimer's disease (Donmez-Altuntas *et al.*, 2005). RORA belongs to the NR1 subfamily of nuclear hormone receptors (Giguère *et al.*, 1995). It may be involved in neuroprotection and cerebellar development, and is a recent candidate gene for autism (Nguyen *et al.*, 2010). Abnormalities in neuroendocrine systems (of which hormone receptors are a component), particularly in the hypothalamic–pituitary–Adrenal Axis, have long been associated with depression (Nemeroff and Vale, 2005). An interaction between a nuclear hormone receptor and proteins involved in nucleolar processes, although speculative at this time, would not be an unreasonable hypothesis to test.

Another subgroup was defined by markers in rs2697992, which occurs in retinoblastoma protein-binding zinc finger (PRDM2), rs6127921, which is approximately 106 kb downstream of bone morphogenetic protein 7 precursor (BMP7), along with rs6046805, which occurs in the open reading frame C20orf26. This subgroup consisted of 128 individuals and had a 69% probability of response. PRDM2 binds to RIZ, a zinc-finger protein which regulates transcription during neuronal differentiation (Buyse *et al.*, 1995). BMP7 has neuroprotective properties (Shen *et al.*, 2008) and can induce oligodendroglial (Tsai *et al.*, 2007) and astrocytic differentiation, thus impairing neuronal migration (Ortega and Alcántara, 2009). These two proteins are therefore involved in the development of cell types in neural tissue whose differentiation is mutually antagonistic, lending face validity to a biological interaction at either the protein or systems level. We caution against overinterpreting the meaning of rules discovered through our statistical process, until they are further confirmed in future studies.

This study has not clarified the underlying genetic underpinnings of response to antidepressants. For scientists, this study provides some new hypotheses to test. This study sheds light on the possible complex biological processes mediating antidepressant response. In contrast to scientists, clinicians focus on one patient at a time.

They do not ask why the medication works but whether it works. If it helps their patient, they are happy to prescribe it. The paradox is that we can help these clinicians improve their prescriptions, even though we are not sure why and how.

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