Anaesthetic Research Society

Vacation Studentship Report 2011

Title

Development and validation of a quantitative phenotype model for malignant hyperthermia susceptibility

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BACKGROUND

Phenotype-genotype analyses strongly suggest that some *RYR1*-variants only partially contribute to malignant hyperthermia (MH) risk. We previously used four separate quantitative phenotypes derived from data collected during the diagnostic *in vitro* contracture testing (IVCT) to explore phenotype-genotype correlations. These previous analyses showed that if we wished to use IVCT data to estimate the contribution of mutations to the MH susceptibility phenotype it would be preferable to develop a composite quantitative phenotype. We have conducted and published a similar study previously but that was confounded by the need to use the IVCT itself to define true positive and true negative cases, thus invoking a circular argument. In this project we used *RYR1* mutation status of individuals from families with identified causative mutations to define "true" positive and negative cases.

REPORT ON RESEARCH UNDERTAKEN

Methods

We selected 301 patients who had undergone IVCT testing and had been tested for a familial *RYR1* mutation associated with MH susceptibility. Using data from 137 of these patients we generated logistic regression probability (backward conditional and forward conditional) models for a composite quantitative phenotype. For construction of each model the dependent variable was *RYR1* mutation status and the predictor variables entered were the pre-drug twitch heights and the muscle contractures at each concentration of test agent for each of the static halothane, dynamic halothane and static caffeine tests (www.emhg.org). The model providing the optimal combination of face validity and best fit was then prospectively validated using the data from the remaining 164 patients. The accuracy of the models was determined using receiver operating characteristic (ROC) curves. SPSS v19.0 (IBM) was used for analyses.

Results

The model generated using the backward conditional algorithm classified 93.6% of cases correctly but the forward conditional model produced fewer anomalies and classified 92.6% of cases correctly. The ROC curves for this model in the two sets of patients are shown in the figure.

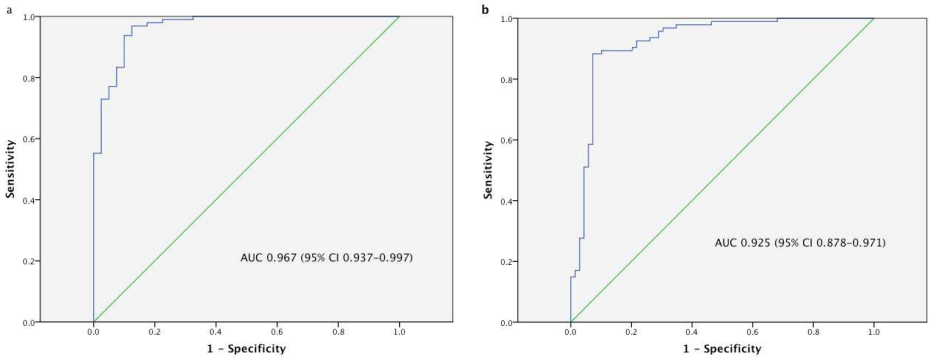

Figure: ROC curves for (a) model generation and (b) test datasets

Discussion

Using the validated model we will next apply quantitative linkage analyses to families with uncharacterized *RYR1* variants in order to estimate the contribution of these variants to the phenotype.

Dissemination

Presented at the ARS winter meeting (28/11/2011). Will form part of a future submission to a peer reviewed journal.

Presentations or publications : as a result of this study.

Abstract in press in the BJA

Will the data from this study lead to any subsequent applications for funding? Please explain.

The data will be used in a MRC Grant application covering the consequences of RYR1 mutations.