A mathematical model to improve on phenotyping for molecular genetic research in malignant hyperthermia

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Author(s) Ginz, Hans F; Rüffert, Henrik; Levano, Soledad; Li Wan Po, Alain; Benthien, Jan; Urwyler, Albert; Girard, Thierry
Author(s) at UniBasel Urwyler, Albert ; Benthien, Jan Philipp ;
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BACKGROUND: The in-vitro contracture test is the standard test to diagnose malignant hyperthermia (MH) susceptibility. Maximum sensitivity is important for patient safety. For scientific purposes, the reduced specificity of contracture testing is a major drawback, and precise phenotyping is of utmost importance. Our study aimed to improve phenotyping for MH susceptibility to more accurately select patients for molecular genetic research in MH, thus, improving the probability to detect novel MH associated variants. METHODS: Patients who underwent contracture and molecular genetic testing were selected from the database of two MH investigation centres (Basel and Leipzig). The area under the curve of halothane and caffeine contracture tests was calculated and a logistic regression model was applied to determine the odds of carrying a MH associated genetic variant. This model was subsequently applied to patients without familial MH related genetic variant. RESULTS: Validation of the logistic regression model showed 98% concordance with molecular genetic results. Among patients with unclear in-vitro contracture test diagnosis (MH equivocal), half of the mutation carriers were classified as positive by the model, whereas 86% of those without familial mutation were classified as negative. Excluding the MH equivocal group, the model showed sensitivity of 0.99 (95% confidence interval: 0.95-0.99) and specificity 0.98 (95% confidence interval: 0.94-0.99), respectively, to identify genetically positive MH individuals. CONCLUSION: Our model is a valuable tool to select patients from MH families for further molecular genetic research. This preselection increases the probability of successful molecular genetic research and is important when available resources are limited.
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