Bayesian modeling to predict malignant hyperthermia susceptibility and pathogenicity of \textit{RYR1}, \textit{CACNA1S} and \textit{STAC3} variants.

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\textbf{Abstract}

\textbf{Aim:} Identify variants in \textit{RYR1}, \textit{CACNA1S} and \textit{STAC3}, and predict malignant hyperthermia (MH) pathogenicity using Bayesian statistics in individuals clinically treated as MH susceptible (MHS).

\textbf{Materials \& methods:} Whole exome sequencing including \textit{RYR1}, \textit{CACNA1S} and \textit{STAC3} performed on 64 subjects with: MHS; suspected MH event or first-degree relative; and MH negative. Variant pathogenicity was estimated using \textit{in silico} analysis, allele frequency and prior data to calculate Bayesian posterior probabilities. \textbf{Results:} Bayesian statistics predicted \textit{CACNA1S} variant p.Thr1009Lys and \textit{RYR1} variants p.Ser1728Phe and p.Leu4824Pro are likely pathogenic, and novel \textit{STAC3} variant p.Met187Thr has uncertain significance. Nearly a third of MHS subjects had only benign variants. \textbf{Conclusion:} Bayesian method provides new approach to predict MH pathogenicity of genetic variants.

\textbf{KEYWORDS:} CACNA1S ; RYR1 ; STAC3 ; contracture test; exome; genetic; malignant hyperthermia; muscle; next-generation sequencing; novel; pathologic

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