The Dravet Prediction tool: predicting patient's phenotypic outcome by combined modeling of *SCN1A* genetic effects with clinical features.

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Background: Mutations in the voltage-gated sodium channel gene (*SCN1A)* are associated with a spectrum of epileptic phenotypes, ranging from 'milder' forms such as genetic epilepsy with febrile seizures plus (GEFS+) to the 'severe' Dravet syndrome (DS) with 30% mortality. With limited performance seizure onset is commonly used as an informal predictor. Currently, there is no systematic predictor for *SCN1A* trajectories and early diagnosis of DS improves prognosis. To date, systematic analysis of genetic variants effects in addition to seizure onset have not been formally addressed.

Methods and Results: Collaborations partners from all around the world help us build the largest set of genetic and clinical data for *SCN1A* patients. A total of 745 *SCN1A* mutation-positive DS (n = 616) and GEFS+ (n=129) patients were included in the analysis. We generated a *SCN1A-specific* genetic score by combining paralog conservation of the affected amino acids with the physicochemical properties of the exchange observed. Next, we trained a generalized linear model using *SCN1A* genetic score and seizure onset as predictors of DS and GEFS+. The *SCN1A* genetic score was positively associated with DS outcome (p-value=4.88×10^{-27}) while seizure onset had a negative significant effect (p-value=3.69×10^{-36}). Taken together the model was effectively able to separate both outcomes (AUC=0.89). We used an additional blind cohort of 277 cases (209 DS and 68 GEFS+) to validate the model. A total of 207 DS cases were correctly predicted, achieving a 90.06% accuracy. We deployed the model into an online tool designed to evaluate any given *SCN1A* patient. The Dravet prediction tool will calculate patient's probability (%) of developing milder GEFS+ or severe DS.

Conclusion: The Dravet prediction tool effectively combines clinical and genetic data to predict the phenotypic spectrum of *SCN1A* variants. Broad collaboration coupled with cost effective computational methods allows the development of novel models with direct clinical applications. Our results can be accessed by doctors from all around the world who can further characterize the expected outcome of S*CN1A* patients and begin treatment.

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Keywords: Dravet syndrome, *SCN1A*, GEFS+, clinical genetics, Neurodevelopmental disorders.