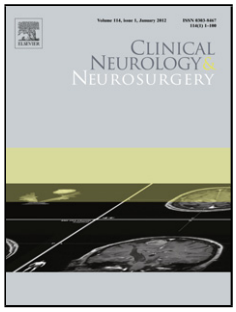

Title: Pathogenic significance of *SCN1A* splicing variants causing Dravet syndrome; improving diagnosis with targeted sequencing for variants by *in silico* analysis

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Pathogenic significance of *SCN1A* splicing variants causing Dravet syndrome; improving diagnosis with targeted sequencing for variants by *in silico* analysis

Running title: Targeted sequencing of *SCN1A* improving diagnosis of infantile epilepsy

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Highlights

- **De novo mutations** in *SCN1A* gene are detected using **Targeted NGS analysis**.
- **Interactome analysis** is helpful to define probable causes of phenotypic variability.
- **A total of 147 mutations** have been reported as splicing ones in *SCN1A* gene.
- **More than 65% of intronic mutations are de novo**.

Abstract

Objectives: Genetic heterogeneity of epileptic encephalopathy (IEE) mandates the use of gene-panels for diagnosis.

Patients and Methods: A 36-gene-panel next-generation sequencing was applied for IEE in two Iranian families. A literature search was performed using keywords to identify reported splicing mutations in *SCN1A* and perform genotype-phenotype correlation.

Results: An update of splicing mutations revealed 147 variants with 65.75% of them *de novo* mutations. Most of the familial variants were of parental origin. The structure of the protein was often