Comparing Mutability of Clinically Significant Voltage-Gated Sodium Channel Subunits

OAKLAND UNIVERSITY WILLIAM BEAUMONT

Ian Armstrong[1], Gustavo Patino MD/PhD.[1,2]

[1]Oakland University William Beaumont School of Medicine

[2]Department of Neurology, Oakland University William Beaumont School of Medicine

Introduction

The voltage gated sodium channel (VGSC) plays a central role in generating action potentials in excitable tissues. The VGSC is a transmembrane protein that contains multiple subunits including a pore-forming alpha subunit and 1-4 additional, non-pore forming beta subunits[6]. As the name suggests, these channels are permeable to sodium when a threshold potential is reached.

The pore-forming alpha subunit has been extensively studied for mutations and clinical correlations. Conversely, the beta subunits of this channel have not been thoroughly explored despite their clinical significance. The 1-4 Beta subunits, coded by genes SCN1B-4B, are auxiliary proteins that perform crucial regulatory functions of the alpha subunit[3]. The regulatory functions of beta subunits include; altering the kinetics of the VGSC, altering the response to voltage or depolarization of the VGSC, regulating VGSC surface expression, or anchoring the VGSC to the membrane[3]. These subunits are also expressed differently in the human body depending on which tissue or organ system a channel is in. The distribution of these proteins further highlights their specialized and important function in the human body.

There have been numerous mutations discovered in the human VGSC that have been implicated in several disease processes. Mutations in the genes coding for β subunits of the VGSC are associated with severe forms of epilepsy, migraine, and other familial conditions[5]. Understanding what clinical conditions are implicated in various SCN mutations is key to understanding targets for therapeutic intervention. As such, understanding the mutability profile of several of these subunits provides knowledge for further avenues of research.

Aims and Objectives

1. Explore the SCN exome sequence for various non-pore forming SCN genes of the VGSC and compile a list of known missense mutations of recorded clinical significance.
2. Compare the rates of mutation between the Beta 1 and Beta 3 subunits (coded by SCN 1B and SCN 3B, respectively) to determine which subunit is more prone to mutations
3. Additionally, record and search missense wild type mutations to see if these mutations are similar in known cancer cell variants of the VGSC

Methods

We compared the frequency of amino acid variants found in patients with known mutations and the general population within the gnomAD database[4], and the variants found in cancer cells from the cBioPortal for Cancer Genomics database[1,2]. This was accomplished by cataloging all known missense mutations as populated by these databases within the SCN1B and SCN3B subunits of the exon coding for the human VGSC.

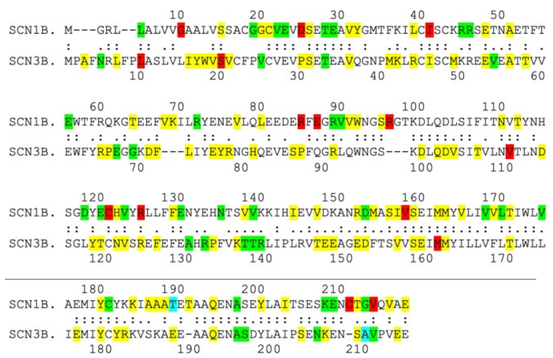
We additionally reviewed primary sequence amino acid variants for both subunits in cancer cells from the cBioPortal cancer genomics database to get a sense of the evolutionary pressures on the different residues.

Results

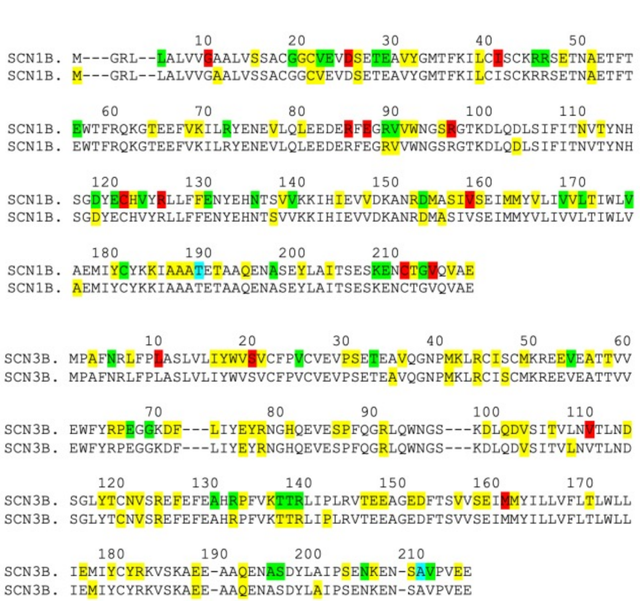
Based on the data from gnomAD both subunits have amino acid variants reported in a similar percentage of the primary sequence (39.4% for β1 and 39% for β3), but pathogenic variants were more common in β1 (5% of residues) than in β3 (1.86%, p=0.065) although not statistically significant. The residues with reported pathogenic variants span the length of both proteins. Interestingly, the pathogenic variants of each subunit occurred in non-overlapping residues, even though some of those residues are conserved between both peptides. Pathogenic variants in β1 was on average 60% more common than those in β3 (frequency 2.35e-4 vs 1.45e-4 correspondingly)[4].

Upon review of the CbioPortal Cancer Genomics database, we found out of 43789 patients with sequencing information for the genes SCN1B and SCN3B (coding for β1 and β3, respectively) 2.2% had non-synonymous variants in β1 and 3.3% in β3 (p=0.002). Only a minority of the residues within each subunit (6.8% in β1 and 9.76% in β3) had a variant reported in cancer cells (p=.276). 4.58% of β1 and 6.51% of β3 residues have variants reported both in human populations and cancer cells. Of the residues reported with pathogenic variants in β1, only one (p.C21) had a variant found in cancer cells, and there were none for β3[1,2].

Key
- Red: Possibly Pathogenic/Conflicting interpretations
- Yellow: No Info
- Green: Uncertain significance



Genetic alignment of SCN1B and SCN3B Exome



SCN 1B & SCN 3B residues in the general population compared with cancer cells (first and second row, respectively)

Conclusions

Our results suggest that the residues with reported pathogenic variants are a non-overlapping set between the two subunits, and might represent key targets for their specialized function. In cancer cells, β3 had a higher mutation load than β1, which is the opposite of that seen in human populations; suggesting different evolutionary pressures on both proteins. One limitation of our study is that we only focused on the main splice variant from the SCN1B and SCN3B genes.

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