Review of: "Conserved patterns across ion channels correlate with variant pathogenicity and clinical phenotypes"

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The authors provide great valuable findings to both medical and scientific community of ion channelopathies, especially human sodium channel epilepsies. In children with epilepsy or DEE associated with sodium channel gene mutations, SCN1A, SCN2A, SCN3A, and SCN8A mutations are pathogenic factors. Among DEE patients, SCN1A is the most common factor. Dravet syndrome is the most common clinical phenotype among DEE caused by sodium channel gene mutations. SCN2A, SCN3A and SCN8A mutation-related DEE may have overlapping phenotypes, and all may have west syndrome. Seizures in children with SCN1A missense mutations is easier to control than those with truncated mutation, suggesting that the type of gene mutation is related to the degree of seizure control. The distribution of missense variants among sodium channel gene mutations revealed that although variants are mainly clustered in homologous domains (particularly the voltage-sensing and pore regions), there is a difference in distribution between SCN1A, SCN2A and SCN8A. Epilepsy-associated SCN1A variants are frequently seen in S5-6 intervening pore loop, which is vital for channel function, whereas only very few SCN2A, SCN88A variants are observed in this region. Voltage-gated sodium channels have a central pore surrounded by four pore-forming modules composed of S5 and S6 segments and an intervening S5-6 pore loop. This loop forms a large extracellular funnel with an ion selectivity filter vital to control ion selectivity.

At present, the exact reason why some missense mutations show severe phenotype is not clear. The clustering of missense mutations in specific fields has also been the object of analysis and controversial interpretation. The enrichment of missense mutations in a specific SCN1A region in patients with Dravet syndrome has been focused. In particular, in the cytoplasmic ring between all four domains (DI to DIV), enrichment of DIII and DIV was found in segment S4 acting as a voltage sensor and segment S5 and S6 acting as a pore ring. However, although mutations in the S5 ~ S6 hole region will lead to complete loss of function, similar to haploid function deficiency, they can be found in Dravet syndrome and GEFS+, so it's difficult to distinguish phenotypes.

However, I am very excited that in this paper, the authors provided a new concept of ion channel biophysical structures and function, indicating that pore axis distance is associated with seizure age of onset and cognitive performance as well as differential GOF and LOF. The concept of pore axis distance may be helpful to understand the different SCNA phenotypes. There are some interesting genetic results and clinical findings. The methods is correct. The results of this study is impressive. However, as a doctor, I am most concerned about treatment, which is also the concern of patients. Therefore, I would like to ask the author to explain how pore axis distance is helpful to the clinical treatment of epilepsy related to sodium channel gene mutation, such as choosing of sodium channel blockers or other ASMs.

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