Abstract: Large-scale human genetic studies have identified SCN2A as one of the leading genes associated with monogenic autism. SCN2A encodes the voltage-gated sodium channel Nav1.2, a main mediator of neuronal action potential firing. The current paradigm suggests that Nav1.2 gain-of-function variants enhance neuronal excitability, resulting in epilepsy, whereas Nav1.2 deficiency impairs neuronal excitability, contributing to autism. However, this paradigm does not explain why ~20%–30% of individuals with Nav1.2 deficiency still develop seizures. Here in this talk, I will discuss our recent work using the gene-trap SCN2A deficient mouse model as well as human induced pluripotent stem cells (hiPSCs) carrying SCN2A genetic mutation to understand SCN2A-related autism and epilepsy. I will also discuss our effort to advance precision medicine for SCN2A disorders.