Sodium Channel α2-subunit (SCN2A) Related Disorder

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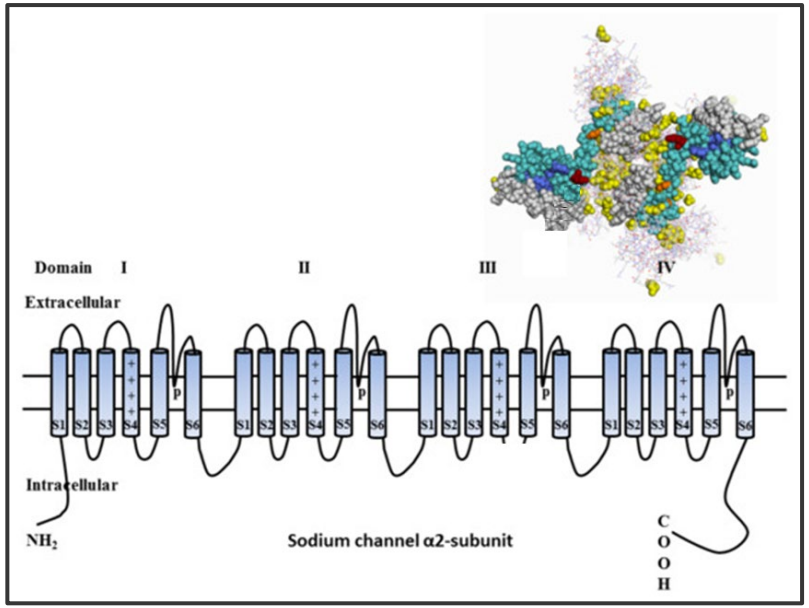
What is SCN2A?

- SCN2A (Sodium Channel α2-subunit) is a gene that encodes a sodium channel protein called Nav1.2.
- Nav1.2 is a transmembrane protein that regulates the flow of sodium ions into neurons in the brain which helps to initiate and propagate action potentials, the electrical signals that allow neurons to communicate with each other.
- Nav1.2 is expressed in various regions of the brain and is involved in a variety of physiological processes, including neurotransmitter release, synaptic plasticity, and the regulation of excitability in neurons.
- This gene and its protein are crucial for proper brain function.



Modified from Griffiths LR et al 2018

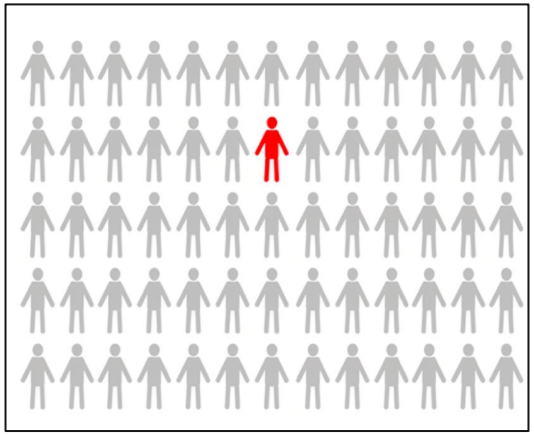
What is a SCN2A-Related Disorder?

- SCN2A-related disorders (SRD) are caused by pathogenic genetic variants that disrupt the proper flow of sodium ions through Nav1.2 in neurons.

- Incidence rate estimates range between ~8 -11 per 100,000 live births (or ~1:9,000 - 12,500 live births)
  (Lal D. et al. Brain 2020 and Bender et al. 2018 Trends in Neuroscience)

- This extrapolates to an estimated US prevalence range between 12,000 – 16,000 patients at current based on conservative lifespan estimates[1] for epilepsy.

- SRD is a complex developmental encephalopathy with distinct and unique clinical features.



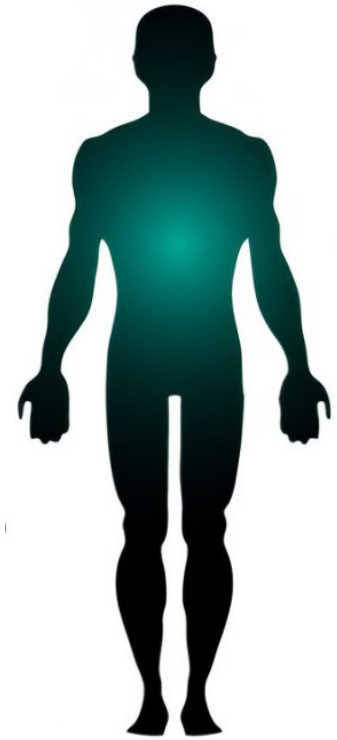
1. Sander et al. 2004

SRD Clinical Characteristics

Common SRD Clinical Characteristics:

Refractory Epilepsy – EIEE, infantile spasms, DEE
Autism Spectrum Disorder – (*leading monogenic cause of autism spectrum disorders*[1]*), behavioral disorders, pervasive developmental disorder*
Movement Disorders – Dystonia, choreiform
Global Developmental Delay and intellectual disability
Gastrointestinal Issues – constipation and GERD
Hypotonia
Autonomic Dysfunction – Arrhythmias, gastrointestinal dysfunction, heat intolerance, neuropathy, urinary retention
Sleep Dysfunction
Cortical Visual Impairment

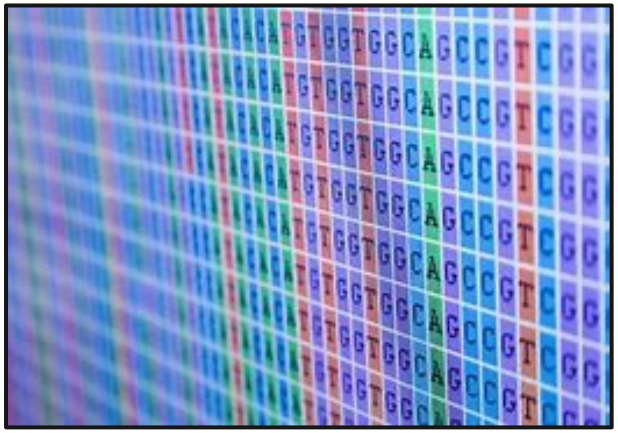
SRD's complex clinical characteristics led to a consistently high risk of morbidity and mortality.



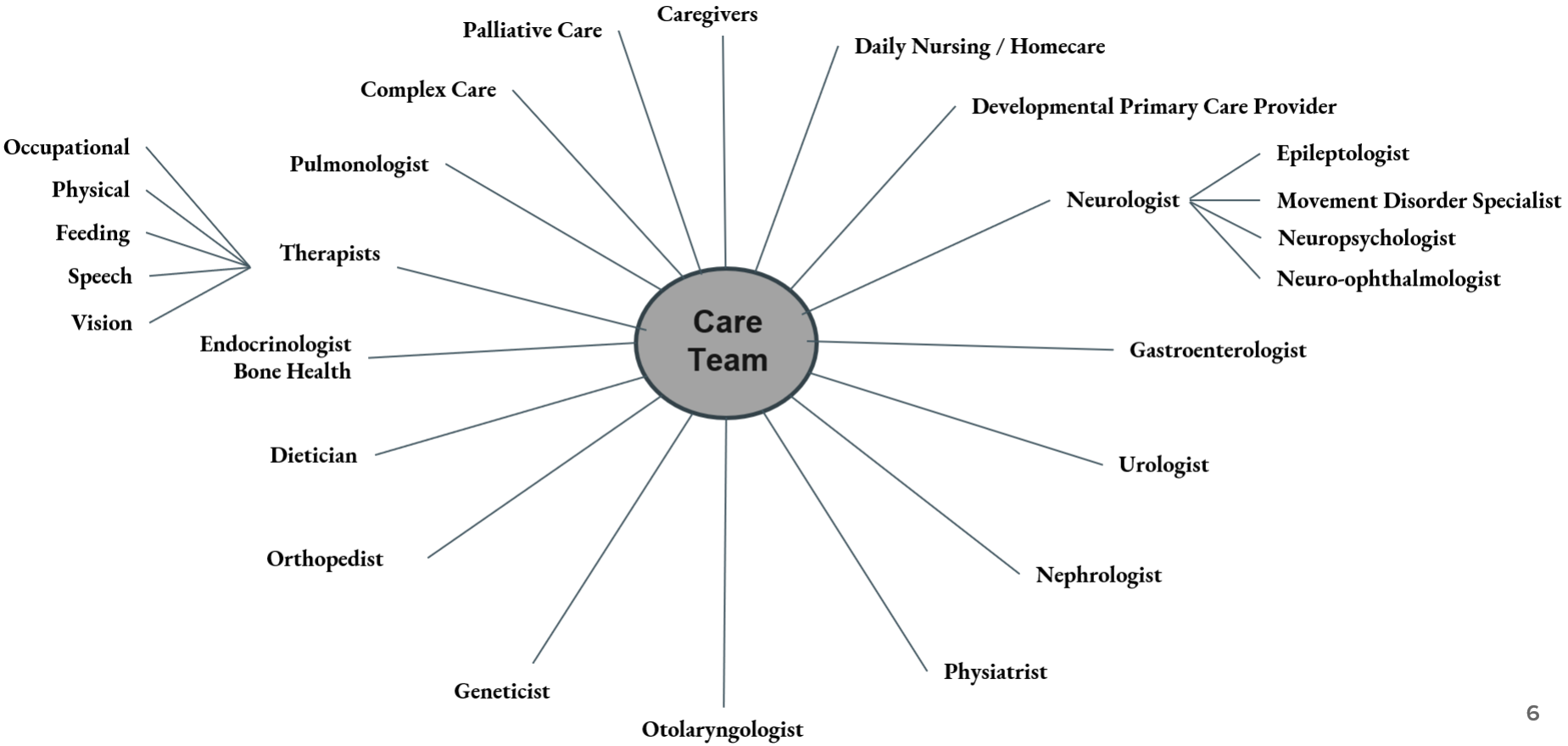
1. Jack M. Fu, et al 2021

How SRD is Diagnosed

- Genetic testing is required to diagnose SRD.
- Common genetic tests are capable of diagnosing SRD.
- SCN2A is on most epilepsy panels.
- Genetic counselors can make an SRD diagnosis but follow up tests and clinical workup can be used to help determine risks and tailor treatment options.



SRD Requires Complex Coordination of Care



Current SRD Treatment Protocols Distinct from Generalized Epilepsy…

SCN2A Treatment Recommendations Based on Age of Seizure Onset

Seizure Onset	Effective Treatment	Contraindicated
< 3 months	**Sodium Channel Blockers:** •Carbamazepine •Oxcabazepine •Phenytoin •Lamotrigine •Lacosamide	Unknown (GABAergic agents?)
> 3 months	**GABAergic Agents:** •Valproic acid •Benzodiazepines •Stiripentol •Cannabidiol	**Sodium Channel Blockers**

Modified from Møller RS et al. 2019

..And Will Likely Continue to be so in the Future

Precision Medications in Development for SCN2A

Sponsor	Status	Precision Medicine Class
Praxis Precision Medicine	Ph1/2 Ready	SCN2A specific Antisense Oligonucleotide
Praxis Precision Medicine	Preclinical	SCN2A specific Antisense Oligonucleotide
Regel Therapeutics	Preclinical	SCN2A specific CRISPR-activation gene therapy

Why The Addition of an SRD Code is Important

Potential Specific Examples of Benefit from a Specific SRD ICD-10-CM code:

- Improved tracking and monitoring in clinical settings and research
- Improved understanding of the multiple system impacts of SRD
- Improved care, more readily providing appropriate treatment, and clinical decision support
- Improved seizure control - with more rapid implementation of appropriate seizure meds
- Improved quality of care, and outcomes
- Decreased hospital stay length
- Better assessment of risk/ reward for different treatments (such as vigabatrin considering risk of cortical visual impairment)
- Faster and more appropriate services post diagnosis (PT, OT, ST, FD, Vision)
- Better appreciation of goals of care
- Better understanding of natural history of the condition
- Better understanding of incidence and prevalence

In Conclusion

SRD is a **unique** and **complex genetic** condition.

SRD should **NOT** be classified as part of any other syndrome.

The medical, academic, and pharmaceutical communities already recognize SRD as distinct clinical condition with distinct clinical needs.

Creation of a unique code will **positively** impact SRD outcomes and quality of care.

A dedicated code is **necessary** to more accurately *identify, assess*, and *manage the complex medical needs* of patients with SRD across the United States.