Seizure Onset, Intractability, and Developmental Outcomes Among Individual with *SCN2A* or *DYRK1A* Mutations

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INTRODUCTION

- Mutations to SCN2A or DYRK1A are associated with autism spectrum disorder (ASD), intellectual disability (ID), and seizures, but the mechanisms by which these mutations contribute to neurodevelopmental disabilities and seizures differ notably (Earl et al., 2017; Sanders et al., 2018)
- Mutations to SCN2A can lead to infant or childhood onset seizures according to their impact on NaV1.2 activity, and mutations to DYRK1A impact multiple aspects of neuronal development (Dang et al., 2018; Sanders et al., 2018; Wolff et al., 2017)
- Among individuals with DYRK1A mutations, febrile seizures in infancy often progress to generalized tonic-clonic seizures (Ji et al., 2015)
- Early seizure onset and seizure intractability generally contribute to poorer developmental outcomes (Thompson & Duncan, 2005; Vasconcellos et al., 2001), but these associations have not yet been examined in individuals with mutations to SCN2A or DYRK1A

METHOD

- Participants were individuals with likely pathogenic mutations to:
  - DYRK1A (n = 26, ages = 4-22 years)
  - SCN2A (n = 19, ages = 2-21 years)
- 65% of participants with a DYRK1A mutation and 27% of participants with a SCN2A mutation had a history of febrile seizures
- 69% of participants with a DYRK1A mutation and 89% of participants with a SCN2A mutation had a history of non-febrile seizures
  - Analyses focused on non-febrile (without fever) seizures, as febrile seizures in children are typically unassociated with epilepsy (Fetveit, 2008)
- Participants seen for phenotyping by ongoing University of Washington study looking at specific genetic events associated with ASD and related developmental disorders
  - Seizure history: Medical History Interview - caregivers reported seizure history, age of seizure onset in months, and whether seizures had been described at intractable (occurring at high frequency or medication resistant)
  - Cognitive functioning: Differential Ability Scale-II and the Mullen - assessed verbal and non-verbal IQ
  - Adaptive functioning: Vineland-II and Vineland-III - measured adaptive behaviors (Adaptive Behavior Composite)
- Analyses:
  - Chi-square and t-tests were conducted to assess whether seizure prevalence, onset, and intractability differed across mutation groups
  - Bivariate correlations and t-tests were conducted to determine whether age of onset and intractability were associated with cognitive and adaptive skills within each gene group

Individuals with *SCN2A* mutations have seizures with an earlier onset and a higher rate of intractability when compared to those with *DYRK1A* mutations.

No significant associations between seizure onset or severity and cognitive or adaptive skills were identified across groups, suggesting that alternate mechanisms might be contributing to variability in developmental outcomes for individuals with mutations in *SCN2A* or *DYRK1A*.

RESULTS - CORRELATIONS

DYRK1A

Variable	*n*	*M*	*SD*	1
1. Seizure Onset Age	18	51	47.31	
2. Verbal IQ	26	42.54	26.92	.23
3. Nonverbal IQ	26	45.81	26.11	.28
4. Vineland	25	54	13.48	-.04

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

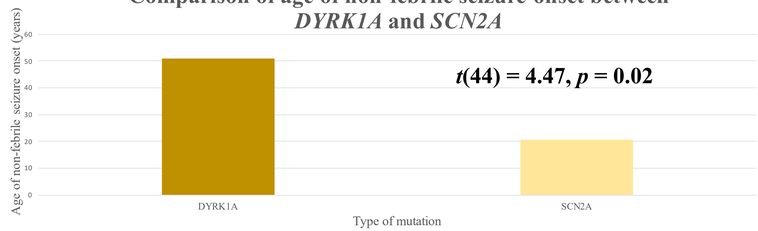
SCN2A

Variable	*n*	*M*	*SD*	1
1. Seizure Onset Age	16	20.44	22.24	
2. Verbal IQ	12	30.5	29.68	-.18
3. Nonverbal IQ	12	31.67	25.43	-.10
4. Vineland	19	45.53	12.77	.17

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

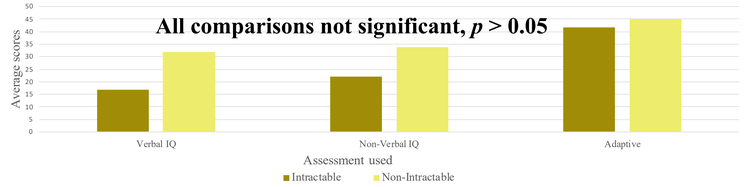
RESULTS - COMPARISONS

Comparison of age of non-febrile seizure onset between *DYRK1A* and *SCN2A*



Comparison of seizure intractability between *DYRK1A* and *SCN2A* individuals

Impact of seizure intractability on cognitive and adaptive skills of SCN2A Individuals



DISCUSSION

- Seizures in individuals with *SCN2A* mutations have earlier onset and greater intractability than in those with *DYRK1A* mutations. This likely reflects the impact of *SCN2A* mutations on sodium channel functioning, which has a strongly established connection to seizure activity
- No significant associations between seizure onset or severity and cognitive or adaptive skills were identified across groups
- These results suggest that alternate mechanisms might be contributing to variability in developmental outcomes for individuals with mutations in *SCN2A* or *DYRK1A*, which could be a topic of future research
- Future research on these genes will better inform individuals and their families of the implications of living with one of these rare genetic mutations

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