Clinical phenotype of *de novo* mutations in *CHD2*

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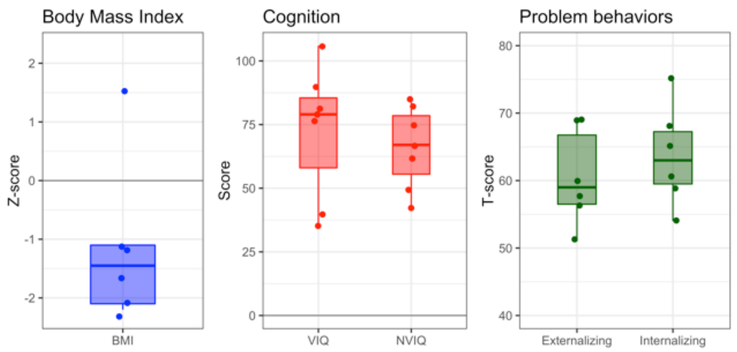
INTRODUCTION

- *De novo* mutations in *CHD2,* a chromatin-remodeling gene, are associated with increased risk for autism spectrum disorder (ASD) and epileptic encephalopathy (Carvill et al., 2013; O'Roak et al., 2014).
- Case reports have identified individuals with *CHD2* mutations who present with neurodevelopmental problems including ASD, intellectual disability (ID), seizures, and challenging behavior, but substantial diversity is present across phenotypes (Chénier et al., 2014; Kim et al., 2018)
- A characteristic physical phenotype of *CHD2* mutations has not been established in humans (Chénier et al., 2014; Kim et al., 2018)
- Quantitative phenotyping of individuals with *de novo CHD2* mutations is necessary to understand how these events contribute to neurodevelopmental disorders and comorbid behavioral and medical problems

METHOD

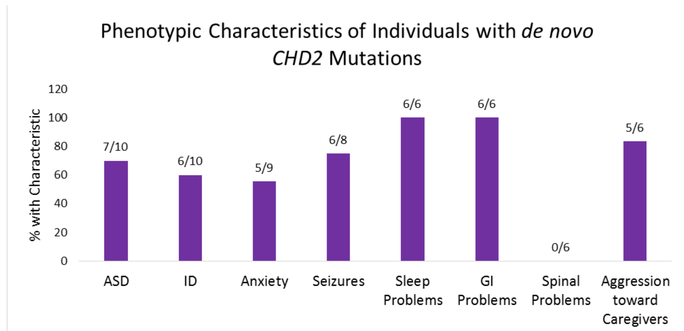
- Participants were 10 individuals with disruptive *de novo CHD2* mutations: Four drawn from an ongoing genetics-first study (TIGER), two from the Simons Simplex Collection (SSC), and four from published studies identified through denovo-db (2018; Epi4K Consortium et al., 2013; O'Roak et al., 2014; Rauch et al., 2012; Willsey et al., 2017).
- Participants in SSC and TIGER completed diagnostic assessments, medical history interviews, and physical and dysmorphology exams

RESULT



De novo CHD2 mutations in humans are characterized by:

- Low BMI
- Sleep and GI problems
- High rates of seizures
- High rates of ASD
- Variability in IQ
- Elevated internalizing and externalizing behavior problems



Demographic Characteristics of Individuals with Disruptive *De Novo CHD2* Mutations

Characteristic	*N*	*Total*	*%*	*M (SD)*	*Range*
Male	5	9	55.56		
White non-Hispanic	7	7	100.00		
Age in months				128.33 (55.06)	72-180
Age at independent walking in months				13.83 (1.72)	12-18
Age at first words in months				22.83 (8.95)	12-36

DISCUSSION

- Low BMI consistent with mouse model of *CHD2* mutations (Kim et al., 2018), while absence of spinal problems is not consistent
- Sleep and GI problems also reported in humans with *CHD8* mutations (Bernier et al., 2014), suggesting that the role of chromatin remodeling in ASD-associated sleep and GI disturbances should be further examined
- Other features (e.g., low body weight and elevated internalizing problems) differ notably from CHD8 phenotype
- Elevated externalizing problems consistent with case reports indicating significant aggression and inattention (Chénier et al., 2014; Thomas et al., 2015)
- Internalizing problems less well established in case reports; some reports of comorbid Tourette syndrome and psychosis (Bernardo et al., 2017; Chénier et al., 2014; Thomas et al., 2015)
- Seizures not present in all individuals with disruptive mutations
- Future directions: Associations between *de novo* mutations and comorbid internalizing disorders; the impact of sleep and GI problems on challenging behavior for individuals with *CHD2* and related mutations