IQSEC2-related Disorder

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Purpose:

Variants in IQSEC2, escaping X inactivation, cause X-linked intellectual disability with frequent epilepsy in males and females. We aimed to investigate sex-specific differences.

Methods:

We collected the data of 37 unpublished patients (18 males and 19 females) with IQSEC2 pathogenic variants and 5 individuals with variants of unknown significance and reviewed published variants. We compared variant types and phenotypes in males and females and performed an analysis of IQSEC2 isoforms.

Results:

IQSEC2 pathogenic variants mainly led to premature truncation and were scattered throughout the longest brain-specific isoform, encoding the synaptic IQSEC2/BRAG1 protein. Variants occurred de novo in females but were either de novo (2/3) or inherited (1/3) in males, with missense variants being predominantly inherited. Developmental delay and intellectual disability were overall more severe in males than in females. Likewise, seizures were more frequently observed and intractable, and started earlier in males than in females. No correlation was observed between the age at seizure onset and severity of intellectual disability or resistance to antiepileptic treatments.

Conclusion:

This study provides a comprehensive overview of IQSEC2-related encephalopathy in males and females, and suggests that an accurate dosage of IQSEC2 at the synapse is crucial during normal brain development.