Clinical exome sequencing identifies two novel *IQSEC2* mutations associated with X-linked intellectual disability with seizures: Implications for genetic counseling and clinical diagnosis

S. Tang1 , S.K. Gandomi1 , K.D. Farwell Gonzalez1 , L. Shahmirzadi1 , J. Mancuso2 , P. Pichurin2 , R. Temme3 , S. Dugan3 , W. Zeng1 . 1) Clinical Genomics, Ambry Genetics, Aliso Viejo, CA., USA; 2) Mayo Clinic, Department of Medical Genetics, Rochester, MN, USA; 3) Children's Hospital & Clinics of Minnesota, St. Paul, MN.

Abstract:

Intellectual disability (ID) is a heterogeneous disorder with a wide phenotypic spectrum. Over 1,700 OMIM genes have been associated with this condition, many of which reside on the X-chromosome. The IQSEC2 gene is located on chromosome Xp11.22 and is known to play a significant role in the maintenance and homeostasis within the neural environment of the brain. Mutations in IQSEC2 have been historically reported as causing nonsyndromic X-linked intellectual disability (XLID) characterized by early onset limited intellectual functioning and limited adaptive behavior. Case reports of affected probands show phenotypic overlap with conditions associated with pathogenic MECP2, FOXG1, CDKL5, and MEF2C gene mutations. Affected individuals, however, have also been identified as presenting with additional clinical features including seizures, autistic-behavior, psychiatric problems, and delayed language skills. Although once thought to be a rare cause of XLID, IQSEC2 mutations are becoming more frequently detected through Next Generation Sequencing technologies utilized in clinical diagnosis. To date, a total of four unrelated families and 32 male probands are reported to carry mutations in this gene. Here we report two novel IQSEC2 de novo truncating mutations (c.2582G>C; p.S861T affecting splicing and c.2052_2053delCG; p.C684X) identified through diagnostic exome sequencing (DES) in two unrelated male probands manifesting developmental delay, seizures, hypotonia, plagiocephaly, and abnormal MRI findings. Both patients also presented with other mild features, not typically seen with IQSEC2 mutations, and neither patient presented with behavioral disturbances as seen in previously reported patients. Our two probands expand on the current understanding of genotype-phenotype correlations that exist for this gene. Our data also suggests that patients with truncating mutations in IQSEC2 are more severely affected compared with previously reported cases known to carry missense alterations. Overall, DES established a molecular diagnosis for two patients in whom traditional testing methods were uninformative while contributing to expanding the mutational and phenotypic spectrum of IQSEC2. In addition, our data clearly supports recently published data suggesting that IQSEC2 plays a more significant role in the development of XLID than previously anticipated. It should also be considered as a candidate gene in cases of male probands presenting with ID plus seizures.