Range of genetic mutations associated with severe non-syndromic sporadic intellectual disability: an exome sequencing study.

Abstract:

The genetic cause of intellectual disability in most patients is unclear because of the absence of morphological clues, information about the position of such genes, and suitable screening methods. Our aim was to identify de-novo variants in individuals with sporadic non-syndromic intellectual disability. In this study, we enrolled children with intellectual disability and their parents from ten centres in Germany and Switzerland. We compared exome sequences between patients and their parents to identify de-novo variants. 20 children and their parents from the KORA Augsburg Diabetes Family Study were investigated as controls. We enrolled 51 participants from the German Mental Retardation Network. 45 (88%) participants in the case group and 14 (70%) in the control group had de-novo variants. We identified 87 de-novo variants in the case group, with an exomic mutation rate of 1.71 per individual per generation. In the control group we identified 24 de-novo variants, which is 1.2 events per individual per generation.
generation. More participants in the case group had loss-of-function variants than in the control group (20/51 vs 2/20; p=0.022), suggesting their contribution to disease development. 16 patients carried de-novo variants in known intellectual disability genes with three recurrently mutated genes (STXBP1, SYNGAP1, and SCN2A). We deemed at least six loss-of-function mutations in six novel genes to be disease causing. We also identified several missense alterations with potential pathogenicity. After exclusion of copy-number variants, de-novo point mutations and small indels are associated with severe, sporadic non-syndromic intellectual disability, accounting for 45-55% of patients with high locus heterogeneity. Autosomal recessive inheritance seems to contribute little in the outbred population investigated. The large number of de-novo variants in known intellectual disability genes is only partially attributable to known non-specific phenotypes. Several patients did not meet the expected syndromic manifestation, suggesting a strong bias in present clinical syndrome descriptions. German Ministry of Education and Research, European Commission 7th Framework Program, and Swiss National Science Foundation.