

Bainbridge-Roper Syndrome ASXL3

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The study aimed at widening the clinical and genetic spectrum of ASXL3-related syndrome, a neurodevelopmental disorder, caused by truncating variants in the ASXL3 gene. In this international collaborative study, we have undertaken a detailed clinical and molecular analysis of 45 previously unpublished individuals with ASXL3-related syndrome, as well as a review of all previously published individuals. We have reviewed the rather limited functional characterization of pathogenic variants in ASXL3 and discuss current understanding of the consequences of the different ASXL3 variants. In this comprehensive analysis of ASXL3-related syndrome, we define its natural history and clinical evolution occurring with age. We report familial ASXL3 pathogenic variants, characterize the phenotype in mildly affected individuals and discuss nonpenetrance. We also discuss the role of missense variants in ASXL3. We delineate a variable but consistent phenotype. The most characteristic features are neurodevelopmental delay with consistently limited speech, significant neuro-behavioral issues, hypotonia, and feeding difficulties. Distinctive features include downslanting palpebral fissures, hypertelorism, tubular nose with a prominent nasal bridge, and low-hanging columella. The presented data will inform clinical management of individuals with ASXL3-related syndrome and improve interpretation of new ASXL3 sequence variants.