

Null variants and deletions in BRWD3 cause an X-linked syndrome of mild-moderate intellectual disability, macrocephaly, and obesity: A series of 17 patients

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Abstract

BRWD3 has been described as a cause of X-linked intellectual disability, but relatively little is known about the specific phenotype. We report the largest BRWD3 patient series to date, comprising 17 males with 12 distinct null variants and 2 partial gene deletions. All patients presented with intellectual disability, which was classified as moderate (65%) or mild (35%). Behavioral issues were present in 75% of patients, including aggressive behavior, attention deficit/hyperactivity and/or autistic spectrum disorders. Mean head circumference was +2.8 SD (2.8 standard deviations above the mean), and mean BMI was +2.0 SD (in the context of a mean height of +1.3 SD), indicating a predominant macrocephaly/obesity phenotype. Shared facial features included a tall chin, prognathism, broad forehead, and prominent supraorbital ridge. Additional features, reported in a minority (<30%) of patients included cryptorchidism, neonatal hypotonia, and small joint hypermobility. This study delineates the clinical features associated with BRWD3 null variants and partial gene deletions, and suggests that BRWD3 should be included in the differential diagnosis of patients with an overgrowth-intellectual disability (OGID) phenotype, particularly in male patients with a mild or moderate intellectual disability associated with macrocephaly and/or obesity.

Keywords: BRWD3; X-linked; intellectual disability; macrocephaly; overgrowth.