A NOVEL NEURODEVELOPMENTAL SYNDROME CAUSED BY LOSS-OF-FUNCTION OF THE ZINC FINGER HOMEOBOX 3 GENE (ZFHX3)

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Intellectual disability (ID) is a very heterogeneous disorder, and hitherto, over 1000 genes have been described to be involved in the etiology of ID. Here, we report on 28 patients with ID and congenital anomalies, and a deletion or protein truncating variant in the ZFHX3 gene. Through a large international collaboration, phenotypical details of all patients were gathered, and the most consistent phenotype of ZFHX3 aberrations has herein been determined by ID, postnatal growth retardation, feeding difficulties and recognizable facial characteristics. *ZFHX3* belongs to the family of zinc-finger homeodomain transcription factors and encodes the ATBF1 protein playing a role in multiple biological processes including tumorigenesis and cell differentiation. It has been previously linked to neural differentiation and shows high expression in the developing human brain, but hitherto has never been linked to intellectual disability. Publicly available and our own data confirm increased expression of ZFHX3 during neural differentiation. Using IP-MS, we identified ZFHX3 interactors belonging to the chromatin remodeling mSWI/SNF complex (BAF complex) and the cleavage and polyadenylation complex (CPC). Further research aims to determine the localization of ZFHX3 in the cell during neural differentiation and to identify the precise role and targets of ZFHX3 in chromatin remodeling and gene transcription. In conclusion our study identified ZFHX3 as a novel gene underlying syndromal ID and revealed novel targets in neuronal differentiation and functioning.