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LOSS OF THE KINETOCHORE PROTEIN BOD1 LEADS TO MENTAL RETARDATION AND OVARIAN FAILURE

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In the course of systematic clinical and molecular studies into autosomal recessive mental retardation (ARMR), autozygosity mapping in a family with four females with mild MR and ovarian failure revealed a single 4.3 Mbp interval on chromosome 5q with a LOD score of 3.8. By sequencing the coding regions of all 27 genes within this region we discovered a nonsense mutation in exon 2 of the *BOD1* gene. This defect co-segregated with the disease and was not found in 720 control chromosomes, and no mutations were detected in any of the other genes in the respective interval. *BOD1* is expressed in a wide range of tissues, including brain and ovary. By RT-PCR, we identified two previously unknown isoforms of BOD1 in control fibroblasts and showed expression of all four transcripts in a variety of brain tissues. Quantitative RT-PCR revealed loss of all BOD1 isoforms in patient fibroblasts, including splice variants that did not contain exon 2. This seems to be due to nonsense mediated decay, as it could be abrogated by cycloheximide treatment of the cells. Absence of BOD1 protein in cells of the patients was confirmed by Western blotting experiments. Live cell imaging and other studies revealed several abnormalities of cell division, in keeping with chromosomal bi-orientation defects observed previously in BOD1 depleted Hela cells (Porter et al. J. Cell Biol. 179:187–197, 2007), which may also provide an explanation for the ovarian failure observed in this family. In addition, pull-down and mass spectrometry have enabled us to identify an interacting protein that links BOD1 to gene regulation, and over-expression studies in primary murine neurons indicate an extra-nuclear localization of BOD1 during interphase. The latter suggests an involvement of BOD1 in neuronal information processing and may provide a clue to the pathogenesis of MR in this condition.