Abnormal centrosome and spindle morphology in a patient with autosomal recessive primary microcephaly type 2 due to compound heterozygous WDR62 gene mutation.

Abstract:
Autosomal recessive primary microcephaly (MCPH) is a rare neurodevelopmental disease with severe microcephaly at birth due to a pronounced reduction in brain volume and intellectual disability. Biallelic mutations in the WD repeat-containing protein 62 gene WDR62 are the genetic cause of MCPH2. However, the exact underlying pathomechanism of MCPH2 remains to be clarified. We characterized the clinical, radiological, and cellular features that add to the human MCPH2 phenotype. Exome sequencing followed by Sanger sequencing in a German family with two affected daughters with primary microcephaly revealed in the index patient the compound heterozygous mutations c.1313G>A (p.R438H) / c.2864-2867delACAG (p.D955As*112) of WDR62, the second of which is novel. Radiological examination displayed small frontal lobes, corpus callosum hypoplasia, simplified hippocampal gyration, and cerebellar hypoplasia. We investigated the cellular phenotype in patient-derived lymphoblastoid cells and compared it with that of healthy female controls. WDR62 expression in the patient's immortalized lymphocytes was deranged, and mitotic spindle defects as well as abnormal centrosomal protein localization were apparent. We propose that a disruption
of centrosome integrity and/or spindle organization may play an important role in the development of microcephaly in MCPH2.