論 文 要 旨

Positional cloning and comprehensive mutation analysis identified a novel KDM2B mutation in a Japanese family with minor malformations, intellectual disability, and schizophrenia

氏　　名　横塚 紗永子

The importance of epigenetic control in the development of the central nervous system has recently been attracting attention. Methylation patterns of lysine 4 and lysine 36 in histone H3 (H3K4 and H3K36) in the central nervous system are highly conserved among species. Numerous complications of body malformations and neuropsychiatric disorders are due to abnormal histone H3 methylation modifiers. In this study, we analyzed a Japanese family with a dominant inheritance of symptoms including Marfan syndrome-like minor physical anomalies (MPAs), intellectual disability, and schizophrenia (SCZ). We performed positional cloning for this family using a single nucleotide polymorphism (SNP) array and whole- exome sequencing, which revealed a missense coding strand mutation (rs1555289644, NM_032590.4: c.2173G>A, p.A725T) in exon 15 on the plant homeodomain of the KDM2B gene as a possible cause of the disease in the family. The exome sequencing revealed that within the coding region, only a point mutation in KDM2B was present in the region with the highest logarithm of odds score of 2.41 resulting from whole genome linkage analysis. Haplotype analysis revealed co- segregation with four affected family members (IV-9, III-4, IV-5, and IV-8). Lymphoblastoid cell lines from the proband with this mutation showed approximately halved KDM2B expression in comparison with healthy controls. KDM2B acts as an H3K4 and H3K36 histone demethylase. Our findings suggest that haploinsufficiency of KDM2B in the process of development, like other H3K4 and H3K36 methylation modifiers, may have caused MPAs, intellectual disability, and SCZ in this Japanese family.