論 文 要 旨

Positional cloning and comprehensive mutation analysis of a Japanese family with lithium-responsive bipolar disorder identifies a novel *DOCK5* mutation

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Bipolar disorder (BD) is a severe psychiatric disorder characterized by the recurrence of depressive and manic episodes. Its heritability is high, and many linkage and association studies have been performed. Although various linkage regions and candidate genes have been reported, few have shown sufficient reproducibility, and none have identified the pathogenic genes based on the results of the linkage analysis. To find functional variants that are expected to be rare and have strong genetic effects, we recruited ten healthy individuals, two individuals with unknown status, and six patients with BD or recurrent major depressive disorder (MDD) from a Japanese family consisting of 21 members. We performed a genome- wide linkage analysis using a 100K single-nucleotide polymorphism (SNP) array and microsatellite markers to narrow linkage regions within this family. Subsequently, we performed whole-exome sequencing for two patients with BD to identify genetic mutations in the narrowed linkage regions. Then, we performed co-segregation analysis for DNA variants obtained from the results of the exome sequencing. Finally, we identified a rare heterozygous mutation in exon 31 of DOCK5 (c.3150A>G, p.E1057G). Convergent functional genomics analysis revealed that DOCK5 was listed as one of the biomarkers for mood state and suicidality. Although DOCK5 is still a functionally unknown gene, our findings highlight the possibility of a pathological relationship between BD and DOCK5.