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Clinical note

Expanding association between *BICD2* variants and brain malformations and associated lissencephaly

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Bicaudal D is an important component of a crucial pathway that involves dynein and dynactin and is responsible for transporting mRNAs and other cellular cargo.[1)] Variants in Bicaudal D2 Drosophila homolog 2 (*BICD2*) were known to be associated with autosomal dominant lower extremity-predominant spinal muscular atrophy 2 (SMALED2A/2B; Online Mendelian Inheritance in Man [OMIM]).[2,3)] After a recent study demonstrating loss of *BICD2* function are associated with brain malformations in human,[4)] 9 patients with *BICD2* variants were reported to be associated with brain malformations.[5-10)] However, only a few patients have been reported to exhibit lissencephaly in brain imaging, and as such, this phenotype has not yet been added to the OMIM database. We report a case of Korean female patient with novel heterozygous *BICD2* variant with developmental regression and lissencephaly, expanding neurologic phenotypic spectrum of *BICD2*-associated disease.

A 9-month-old female patient visited our outpatient clinic due to developmental delay. At the initial visit, she demonstrated eye contact, social smiles and head control, but was unable to sit unassisted. In neurological examination, spasticity and increased deep tendon reflexes were observed. Facial dysmorphism and joint abnormalities were not noted. Initial examination also revealed microcephaly, as head circumference measured 40.5 cm (-3.7 standard deviation). A brain magnetic resonance imaging taken at 9 months of age showed lissencephaly and corpus callosum hypogenesis (Fig. 1A). Routine laboratory tests, including creatine kinase, showed no notable abnormalities or neutropenia. During follow-up, she was able to sit alone at 14 months of age, crawl at 2 years of age, stand with assistance at 3 years of age, and understand a few commands. However, her developmental milestones regressed when she was 3.5 years old. The initial seizure occurred at 30 months of age, characterized by generalized seizures. A routine baseline electroencephalogram (EEG) at 16 months showed frequent repetitive beta activities, and the EEG at the onset of the first seizure revealed irregular high amplitude delta waves with a few suspicious frontal sharp waves. Initial treatment with valproic acid (up to 70 mg/kg/day) was followed by levetiracetam (up to 50 mg/kg/day) and topiramate (up to 50 mg/kg/day), but was still refractory. At 7 years old, the patient can only sit with assistance and does not understand commands. An EEG taken at 7 years old showed an excessive amount of high amplitude irregular delta waves and some suspicious frontal sharp waves. The patient still suffers from 2–5 generalized seizures per day and did not gain any developmental milestones.

Trio whole exome sequencing (WES) was performed. The detailed method for data generation and processing was described elsewhere.[11)] Initial trio WES analysis did not result in likely pathogenic/pathogenic variants linked to patient's phenotype, as *BICD2* was reported to be associated with only spinal muscular atrophy phenotype and not with severe developmental delay and/or lissencephaly. A recent WES reanalysis revealed a novel *de novo BICD2* variant (c.2324_2327dupAGAA [p.Thr777fs]) as a likely pathogenic variant with subsequent Sanger sequencing confirmation (Fig. 1B). All known *BICD2* variants associated with brain malformations is shown in Fig. 1C.

Written informed consent-to-disclose was obtained from the parent of the patient. The study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. 2010-125-1166).

BICD2 is vital for cerebral cortex development.[4)] Only 9 patients with *BICD2* variants were reported to have brain malformations (hypogenesis of corpus callosum, polymicrogyria, cerebellar hypoplasia, white matter loss and ventriculomegaly), including lissencephaly in 3 patients. Notably, microcephaly was observed in all *BICD2*-related lissence-

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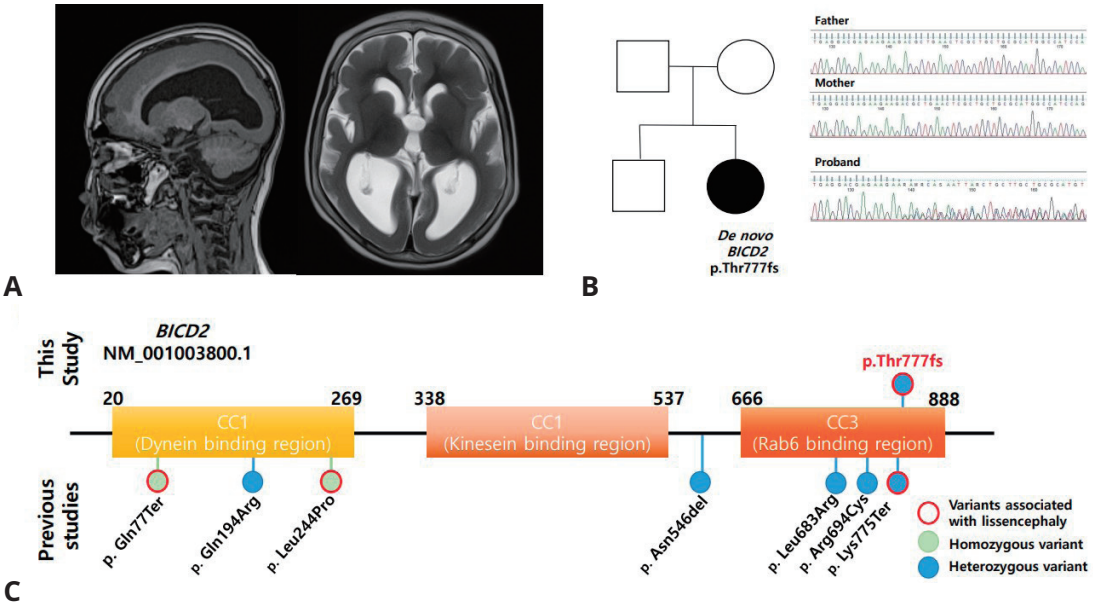

Fig. 1. Radiogenomic findings of patients with *BICD2*-associated brain malformations in this study. (A) Brain magnetic resonance imaging findings of this patient with lissencephaly and hypogenesis of the corpus callosum (left: T1 sagittal; right: T2 axial). (B) Patient's pedigree and variant information. Trio-sanger sequencing was performed to confirm the variant. (C) All reported *BICD2* variants associated with brain malformations to date. Variants associated with lissencephaly are marked in red.

Table 1. Clinical phenotypes of patients with *BICD2* variant-associated brain malformations

Variable	Patient 15	Patient 26	Patient 36	Patient 47	Patient 57	Patient 68	Patient 74	Patient 89	Patient 910	This study
Sex	Male	Male	Male	Female	Male	Female	Male	Female	Male	Female
Age at last examination	7 Years	4 Years	45 Days	12 Years	6 Years	4 Months	4 Years	12.6 Years	2 Years	7 Years
Microcephaly	No	Yes	No	No	No	No	Yes	Yes	Yes	Yes
Facial dysmorphism	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No
Intellectual disability	No	Yes	N/A	Yes	Yes	N/A	Yes	Yes	Yes	Yes
Arthrogryposis/ contracture deformities	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No
Seizures	No	No	No	Yes	Yes	No	No	No	Yes	Yes
Brain MRI findings										
Lissencephaly/pachygyria	No	No	No	No	No	No	Yes	Yes	Yes	Yes
Hypogenesis of CC	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Polymicrogyria	No	Yes	Yes	No	No	No	No	No	No	No
Cerebellar hypoplasia	Yes	Yes	Yes	No	No	No	No	No	Yes	No
White matter loss	No	Yes	Yes	Yes	Yes	No	No	No	N/A	No
Ventriculomegaly	No	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes
Peripheral neuropathy	Yes	Yes	Yes	N/A	N/A	Yes	No	No	No	No
Developmental regression	No	No	No	No	No	No	No	No	No	Yes
Zygosity	Het	Het	Het	Het	Het	Het	Het	Hom	Hom	Het
BICD2 variant	c.2048T>G (p.Leu683Arg)	c.2080C>T (p.Arg694Cys)	c.2080C>T (p.Arg694Cys)	c.1636_1638 delAAT (p.Asn546del)	c.1636_1638 delAAT (p.Asn546del)	c.581A>G (p.Gln194Arg)	c.2323A>T (p.Lys775Te)	c.731T>C (p.Leu244 Pro)	c.229C>T (p.Gln77Ter)	c.2324_2327 dupAGAA (p.Thr777fs)

MRI, magnetic resonance imaging; CC, corpus callosum; Het, heterozygous, Hom, homozygous; N/A, not available.

phaly cases unlike other *BICD2*-related brain malformations, while arthrogryposis commonly found in *BICD2*-related SMALED2A/2B patients was rare in lissencephaly patients. Our patient exhibited microcephaly and lissencephaly, consistent with previous studies.[4,9,10] We observed developmental regression in our patient, a novel occurrence in *BICD2*-related disease patients during long-term follow-up until age 7 (Table 1). We suspect it may result from refractory seizures not reported before.

We observed significant findings in understanding phenotype-genotype correlations of *BICD2*-related disorders. Most brain malformation-associated *BICD2* variants occur in the

conserved CC3 domain. Lissencephaly-related variants are typically heterozygous nonsense variants (p.Lys775Ter) in CC3 or homozygous variants (p.Leu244Pro and p.Gln77Ter) in CC1. Our patient's out-of-frame duplication variant in CC3 (p.Thr777fs) suggests that high-impact variants in CC3 and/or bi-allelic variants in other domains may contribute to the lissencephaly phenotype in *BICD2*-related disorders. No nonsense or out-of-frame deletion/duplication *BICD2* variants associated with SMALED2A/2B phenotypes have been reported in the ClinVar database to date.[12] A recent study revealed interactions between the CC3 domain of *BICD2* and 2 nuclear envelope-associated cargos, RanBP2 and Nesprin-2, in neuronal precursor cells in the developing brain. This finding suggests potential phenotype-genotype correlations with variants located in the CC3 domain.[13]

In summary, we report a case of novel *de novo* heterozygous *BICD2* variant-associated with lissencephaly and developmental regression. Given that lissencephaly phenotype has not yet been incorporated in the OMIM database, our case significantly contributes to the expanding phenotypic spectrum of *BICD2*-associated diseases and highlights the importance of raising awareness of the phenotypes reviewed in our study.

Footnotes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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