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Case Report

Familial pachygyria in both genders related to a *DCX* mutation

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Abstract

Doublecortin (DCX) and tubulin play critical roles in neuronal migration. *DCX* mutations usually cause anterior dominant lissencephaly in males and subcortical band heterotopia (SBH) in females. We used whole-exome sequencing to investigate causative gene variants in a large family with late-childhood-onset focal epilepsy and anterior dominant pachygyria without SBH in both genders. Two potential variants were found for the genes encoding DCX and beta tubulin isotype 1 (TUBB1). The novel *DCX* mutation (p.D90G, NP_000546.2) appeared to be a major causative variant, whereas the novel mutation of *TUBB1* (p.R62fsX, NP_110400.1) was found only in patients with more-severe intellectual disability after gender matching. We report an unusual *DCX*-related disorder exhibiting familial pachygyria without SBH in both genders.

Keywords: Pachygyria; Focal seizures; *DCX*; Genetics; Intellectual disability

1. Introduction

Mutations of the gene encoding doublecortin protein (DCX) cause frontally pronounced classic lissencephaly in hemizygous male patients, and subcortical band heterotopia (SBH) in heterozygous females [1–3]. Females with *DCX* mutations rarely exhibit classic lissencephaly and can have normal brain imaging findings [1,4]. In male patients with agyria or pachygyria, seizures usually begin during infancy, manifesting as spasms [2,3]. However, other types of epilepsy have been reported intermittently, such as Lennox–Gastaut syndrome or milder forms of epilepsy in male patients with SBH [4,5]. Nevertheless, familial focal epilepsy associated with pachygyria in both genders has not yet been reported in *DCX*-related disorders. We report herein a novel missense mutation of *DCX* resulting in late-childhood-onset familial focal epilepsy and anterior dominant pachygyria without SBH in both genders.

2. Case reports

2.1. Patients

In this family with familial focal epilepsy and anterior dominant pachygyria without SBH in both genders, sei-

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zures started after 5 and 10 years in the affected male and female patients, respectively (Fig. 1). Seizures in each patient were stereotypically focal tonic or dystonic with or without loss of consciousness. Generalized seizures were rarely observed. No spasms, atypical absence, nocturnal tonic seizures, or drop attacks were seen. Seizures did not occur in clusters, did not progress into status epilepticus, and usually lasted for less than 3 min. In electroencephalography, epileptiform discharges or slowing were frequently seen from the bilateral frontal areas. Unilateral or bilateral temporal, central, or parietal discharges were also observed. However, no generalized discharges were noted. Brain magnetic resonance imaging (MRI) of male patients demonstrated generalized pachygyria that was worse anteriorly (grade 4b1) [2]. In female patients, mild forms of asymmetric or symmetric anterior pachygyria with normal posterior gyri (grade 4b2) were observed without SBH (Fig. S1). Developmental slowing was identified in male patients aged between 16 and 20 months. In female patients with intellectual disability, their slowing was identified after school entrance. Neurologic signs of tremor or poor fine motor function were observed only in male patients (Table 1).

2.2. Molecular genetic analysis

Whole-exome sequencing (WES) was performed in two affected male cousins (III-2 and III-9) and one unaffected sibling (III-8), using the TruSeq Exome Kit (Illumina) on a HiSeq2000 (Illumina) platform. A novel missense mutation of *DCX* (p.D90G, NP_000546.2) was found under the X-linked model using our systematic bioinformatics analyses (Fig. S2). Of the two remaining variants found under the autosomal dominant model, a novel nonsense mutation of the gene encoding the beta tubulin isotype 1 (TUBB1; *TUBB1*; p.R62fsX, NP_110400.1) was uniquely expressed in the human brain and was predicted to be disease-causing (Table 2). Neither the *DCX* nor the *TUBB1* variant was found in any of the following SNP databases: the 1000 Genomes Project, the Single Nucleotide Polymorphism Database, the National Heart, Lung, and Blood Institute Exome Sequencing Project, the Korean Single Nucleotide Polymorphism Database (400 normal Korean controls; http://nih.go.kr/NIH_NEW/main.jsp, Korean) and our in-house database (100 normal Korean controls).

The *DCX* and *TUBB1* variants were reverified by Sanger sequencing in the three WES samples (Fig. S3). Genotyping of the two variants in 200 neurologically normal Korean subjects by the high-resolution melting technique (HRM) found no same mutations. Direct sequencing of the novel *DCX* mutation in other 9 blood samples from this family revealed the same variant only in patients and female carriers. The *TUBB1* mutation was identified only in female patients with intellectual disability and in male patients with severe intellectual disability (Fig. 1 and Table 1).

This study was approved by the Human Research Ethics Committee of the Chonnam National University Hospital (CNUH). Informed consent for participation was obtained from the parents or guardians of minors and adult patients with intellectual disability. The biospecimens for this study were provided by the CNUH Biomedical Research Institute Biobank. All samples

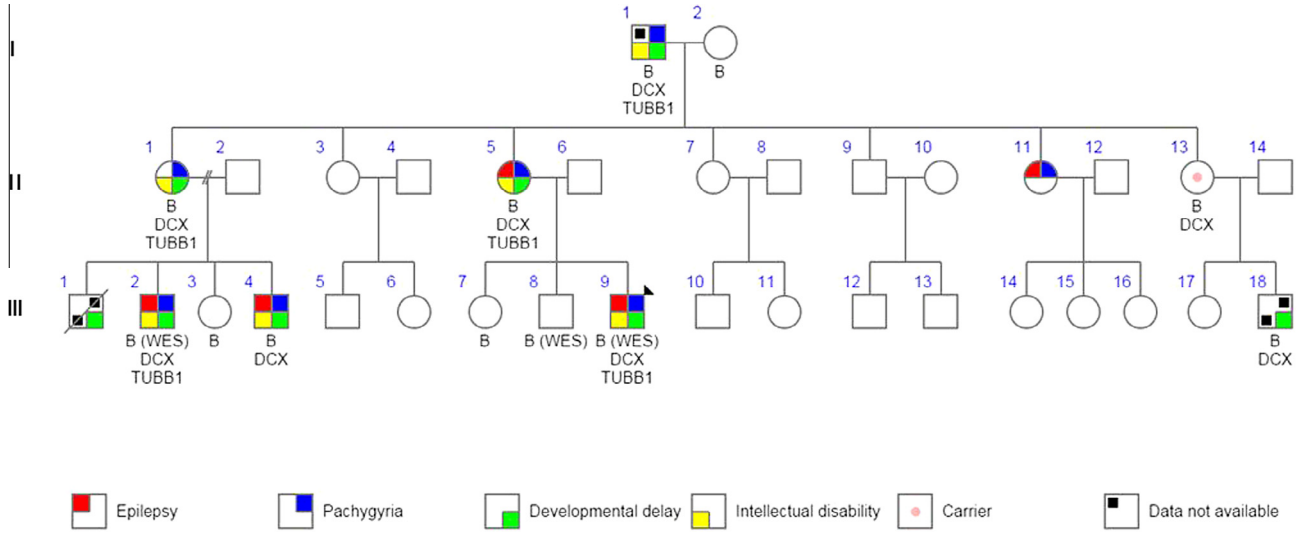

Fig. 1. Family pedigree of the large family investigated in this study with late-childhood-onset familial focal epilepsy and anterior dominant pachygyria without subcortical band heterotopia in both genders. The arrowhead indicates the proband. Abbreviations: B, blood available for study; DCX, the novel mutation in exon 2 of the gene encoding doublecortin (c.269A>G, NM_000555.3; p.D90G, NP_000546.2); TUBB1, the novel mutation in exon 3 of the gene encoding beta tubulin isotype 1 (c.184C>T, NM_030773.3; p.R62fsX, NP_110400.1); WES, whole-exome sequencing.