A homozygous loss-of-function variant in BICD2 is associated with lissencephaly and cerebellar hypoplasia

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INTRODUCTION

Dominant missense variants in the Bicaudal D2 Drosophila homolog 2 (BICD2) gene were initially described in autosomal dominant lower extremity-predominant spinal muscular atrophy 2 (SMALED2A;MIM#618291) [1] and its prenatal onset form (SMALED2B, MIM #618291) [2]. Subsequent reports linked heterozygous BICD2 variants to hereditary spastic paraplegia [3] and developmental brain malformations [4, 5]. Recently, a homozygous BICD2 variant was reported in a girl with Cohen-Like syndrome and other cellular cargoes as part of an essential pathway involving dynein and dynactin [7]. Loss-of-function in BicD2 was associated with defects in neuronal migration in the developing rat brain. It was postulated that defects in nuclear translocation that occur in the post-mitotic neuronal migration stage to be the mechanism of lissencephaly resulting from BICD2 truncating variant [5].

We describe a novel lissencephaly and cerebellar hypoplasia disease and associate it with a recessive variant in the BICD2 gene. Therefore, expanding the phenotypic spectrum of biallelic BICD2-associated disorders.

CLINICAL REPORT

Our patient is the second child of healthy consanguineous (first cousins) Egyptian parents. The pregnancy history was uneventful but prenatal ultrasound in the 30th week of gestation showed intrauterine growth retardation with small biparietal diameter. A male child was born at term by spontaneous vaginal delivery. His birth weight and OFC were 1800 g (−3 SD) and 30 cm (−3 SD), respectively. On physical examination at the age of 7 months, weight was 5800 g (−2.6 SD), length was 64 cm (−1.7 SD), and OFD was 35.5 cm (−5 SD). The EEG done at this time showed theta delta waves with minimal fast beta activity. He had plagiocephaly, almond shaped eyes, thick eyebrows, upturned nostrils and low set ears with thick ear lobules. Brain MRI (Fig. 1) showed lissencephaly, hypogenesis of corpus callosum, cerebellar hypoplasia. At the age of 24 months, his weight, length and OFC were 6500 g (−4.5 SD), 75 cm (−3.3 SD) and 36.5 cm (−8.4 SD), respectively. At that age, he developed partial seizures that showed good response to levetiracetam. He had profound psychomotor delay. Neurological examination showed spasticity of the extremities and increased deep tendon reflexes and positive Babinski. Mild flexion contractures of the knee and clenched hands were noted. Prominent premaxilla, flat philtrum, thin lips, mandibular micrognathia and high arched palate were evident in oro-dental examination. Ultrasound examination of the abdomen revealed left moderate hydronephrosis. Bilateral optic atrophy was found in ophthalmologic examination. Complete blood picture showed normal results. He had male karyotype 46,XY. FISH (fluorescent in-situ hybridization) studies were performed, which ruled out 17p13.3 deletion.

Exome sequencing (detailed method in Supplementary material) identified a homozygous stop gain variant in exon 1 of the BICD2 gene NM_001003800.1: c.229 C>T: p.(Gln77Ter) as the likely causative gene of the patient’s phenotype. Based on the position of the variant, it is most likely led to nonsense-mediated decay. Unfortunately, we did not investigate the effect of the identified variant. The identified variant is not found in public genetic databases or our inhouse database of more than 500 exomes of cases with neurodevelopmental disorders and brain malformations. Segregation analysis using Sanger sequencing confirmed that both parents are heterozygous for the variant.
According to ACMG recommendations of variant classifications: the c.229 C > T p.(Gln77Ter) variant is detected as PVS1, PM2 and therefore classified as a “Likely Pathogenic”. No other disease-causing variants in previously reported genes, associated with his phenotypic spectrum, were identified. Moreover, the large-scale CNV (Supplementary material) data were further analyzed and no disease-causing large duplications or deletions within coding regions were identified.
# Table 1. The clinical findings and variants identified in patients with BICD2 and brain anomalies

|                          | Fiorillo et al. [13] | Ravenscroft et al. [4] | Koboldt et al. [8] | Storbeck et al. [2] | Tsai et al. [5] | Caglayan et al. [6] | This study |
|--------------------------|----------------------|------------------------|--------------------|---------------------|-----------------|---------------------|------------|
|                          | Patient 1  | Patient 2     | Patient 1   | Patient 2    |                 |                     |            |
| **Gender**               | Male       | Male          | Female     | Male        | Female          | Female              | Male       |
| **Age at last examination** | 7 Y       | 4 Y           | 45 days    | 12 Y        | 6 Y             | 4 M                 | 4 Y        |
| **Microcephaly**         | −         | −             | −          | +           | −               | −                   | −          |
| **Abnormality of the ear** | −         | −             | −          | +           | −               | −                   | −          |
| **Almond shaped eyes**   | −         | −             | −          | −           | −               | −                   | −          |
| **Micrognathia**         | −         | +             | +          | −           | +               | −                   | +          |
| **High arched palate**   | −         | −             | −          | −           | −               | −                   | +          |
| **DQ/IQ**                | Normal     | Severe       | NA         | Severe      | Severe          | Severe              | Severe     |
| **Anthrogryposis/contracture deformities** | +         | +             | +          | +           | +               | −                   | + (contractures in the knees) |
| **Seizures**             | −         | −             | −          | −           | −               | −                   | −          |
| **Lissencephaly/Polymicrogyria** | −       | −             | −          | −           | −               | −                   | −          |
| **Hippocampus**          | −         | −             | NA         | −           | −               | −                   | −          |
| **Hypogenesis of corpus callosum** | −       | +             | +          | +           | +               | −                   | +          |
| **Polymicrogyria**       | −         | +             | +          | −           | −               | −                   | −          |
| **Cerebellar hypoplasia** | +         | +             | −          | −           | −               | −                   | −          |
| **White matter loss**    | −         | +             | +          | +           | (near complete absence) | −                   | −          |
| **Ventriculomegaly**     | −         | +             | +          | −           | + (marked)      | −                   | −          |
| **Peripheral neuropathy** | +         | +             | NA         | −           | −               | −                   | −          |
| **BICD2 domain**         | CC3       | CC3           | CC3        | Outside CC2 | Outside CC2    | CC1                 | CC1        |
| **Zygosity**             | Heterozygous | Heterozygous  | Heterozygous | Heterozygous | Heterozygous    | Heterozygous         | Homozygous |
| **Variant**              | c.2048 T > G (p.Leu683Arg) | c.2080 C > T (p.Arg694Cys) | c.2080 C > T (p.Arg694Cys) | c.1636_1638delAAT (p.Asn546del) | c.1636_1638delAAT (p.Asn546del) | c.581 A > G (p.Gln194Arg) | c.731 T > C (p.Leu244Pro) | c.229 C > T (p.Gln777Ter) |

NA not available, M month, Y year, CC1 coiled coil domain 1, CC2 coiled coil domain 2, CC3 coiled coil domain 3
DISCUSSION

The identified variant p.(Gln77Ter) is new and absent from the Genome Aggregation Database. It was evidenced that pathogenic variants in BICD2 are extremely rare in the population, predicted to be damaging by most tools, and occur in specific hotspots within key BICD2 functional domains [8]. Furthermore, WES did not identify any variant(s) in any of the OMIM genes with an acknowledged disease association (including VPS13B gene). Although BICD2 is essential for the proper development of the cerebral cortex [5] but there have been no other clinical reports of individuals with loss-of-function variants in BICD2 showing lissencephaly and cerebellar hypoplasia. However, lissencephaly and cerebellar hypoplasia are consistent with that observed after BICD2 knockdown in mice showing defects in laminar organization of the cerebral cortex, hippocampus and cerebellar cortex, indicative of radial neuronal migration defects. Cell-specific inactivation of BICD2 in astrocytes and neuronal precursors revealed that radial cerebellar granule cell migration is non-cell-autonomous and intrinsic to cerebellar Bergmann glia cells [9, 10]. Therefore, we considered BICD2 to be a convincing candidate gene in the context of lissencephaly and cerebellar hypoplasia. The absence of homozygous loss of function BICD2 variants in the healthy family members supports the clinical relevance of BICD2.

Recently, biallelic variant c.731 T > C p.(Leu244Pro) in BICD2 was described in a girl with abnormal gyral pattern in fronto-temporoparietal regions [6] (Table 1). The girl displayed additionally moderate intellectual disability and Cohen-like features [6]. In comparison, our patient showed congenital microcephaly, profound delay, seizures, lissencephaly and cerebellar hypoplasia. Unlike the patient with Cohen-like features, our patient showed spasticity and developed contracture deformities and did not show neutropenia. Interestingly, a heterozygous missense variant c.2080 C > T, p.(Arg694Cys) was reported in two unrelated patients with mild perisylvian polymicrogyria, and mild cerebellar vermis hypoplasia [4]. Moreover, a BICD2 nonsense variation p.(Lys777Ter) was identified in a boy with lissencephaly and subcortical band heterotopia [5]. These heterogeneous variants are located within the highly conserved CC3 domain of BICD2 (Table 1). Nevertheless, the heterozygous missense variants within the CC1 domain were not associated with abnormalities of cortical development but even showed a milder course of SMAED2A and a higher frequency of foot deformities [8]. Indeed, a larger cohort is required to draw conclusions regarding genotype-phenotype correlations.

Lissencephaly and cerebellar hypoplasia noticed in our patient appeared similar to those with LIS1 variants. This is not surprising as LIS1 interacts with the dynein/dynactin complex and BICD2 to recruit cellular structures [11]. In the mean time, these brain MRI features may overlap with RELN-mutated patients phenotype. However, the cortical migration defect was more severe in our patient than in RELN-mutated patients. In addition, our patient had mild cerebellar hypoplasia unlike RELN-mutated patients who had profoundly hypoplastic and dysplastic cerebellum with no identifiable folia [12].

Our study provides valuable findings into human developmental brain malformations disorders associated with definitive loss-of-function variants in BICD2.

DATA AVAILABILITY
The data that support the findings of this study are available with the corresponding authors upon reasonable request.

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AUTHOR CONTRIBUTIONS
GMH-S and MG recruited the patient into the study and performed the deep clinical characterization. MSA-H performed the research analysis of the exome date, the Sanger sequencing and segregation analysis. MME performed the chromosomes and FISH studies. ISMS performed the oro-dental examination. GMHA-S and MSA-H reviewed and approved the final version of the manuscript. All authors reviewed and approved the final version of the manuscript.

FUNDING
Open access funding provided by The Science, Technology & Innovation Funding Authority (STDF) in cooperation with The Egyptian Knowledge Bank (EKB).

COMPETING INTERESTS
The authors declare no competing interests.

ADDITIONAL INFORMATION
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s10038-022-01060-x.

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