Clinical course of epilepsy and white matter abnormality linked to a novel DYRK1A variant

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Epilepsy and white matter abnormality have been reported in DYRK1A-related intellectual disability syndrome; however, the clinical course has yet to be elucidated. Here, we report the clinical course of an 18-year-old male with a novel heterozygous DYRK1A variant (NM_001396.4: c.957C>G, p.Tyr319*); based on previous reports, epilepsy with this syndrome tends to be well controlled. Follow-up MRIs of the patient’s lesion revealed slightly reduced signal intensity compared to the first image.

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Dual-specificity tyrosine-phosphorylation-regulated kinase (DYRK) catalyzes the phosphorylation of serine and threonine residues on exogenous substrates, as well as the phosphorylation of tyrosine residues within its own activation loop [1]. The DYRK1A gene (NM_001396.4) encodes a member of the DYRK family. DYRK1A is located on chromosome 21q22.13, which is in the Down syndrome critical region of the chromosome [2]. The DYRK1A protein is essential for neurogenesis, neuronal differentiation and proliferation, the cell cycle, and synaptic plasticity [1]. Patients with the DYRK1A pathogenic variant show “mental retardation, autosomal dominant 7” (MIM #614104), which is also called DYRK1A-related intellectual disability syndrome. In addition to intellectual disability, other frequently occurring features include intrauterine growth restriction, feeding difficulties with failure to thrive, microcephaly, seizures, dysmorphic facial features, and developmental delays [2, 3]. Epileptic events and data from magnetic resonance imaging (MRI) assessments have been reported for patients with DYRK1A-related intellectual disability syndrome; however, the clinical course is not well understood.

The index patient was an 18-year-old male who had been born to nonconsanguineous parents at 40 weeks and 6 days. The family history included no reports of intellectual disability, developmental delay, or epilepsy. At birth, his weight was 2604 g (−2.2 SD), his body length was 44.5 cm (−2.9 SD), and his head circumference was 30.5 cm (−1.3 SD), and his head circumference was 51.8 cm (−3.2 SD). The T2/FLAIR high-intensity lesion on MRI gradually disappeared entirely at the age of 3 years and 6 months. At the age of 7 years and 1 month, he discontinued valproate at his parents’ discretion. At 7 years and 2 months, he experienced his first nonfebrile general tonic seizure with cyanosis. After he resumed valproate, his seizure episodes ceased. At 12 years and 2 months, his valproate dose was gradually tapered off, but generalized clonic seizures occurred at the age of 12 years and 8 months. The patient resumed valproate, and his seizure episodes ceased. After 4 years without seizure episodes, valproate was gradually tapered off by age 17. Generalized seizures recurred three months later; accordingly, the same 400 mg dose of valproate was resumed. The patient had undergone interictal electroencephalography (EEG) multiple times since early childhood, but there were no abnormal findings. His first head MRI, taken at the age of 11 years, showed multiple T2/FLAIR high-intensity lesions in white matter and slightly enlarged ventricles (Fig. 1A–D and I). MRI showed no morphological abnormalities in the corpus callosum or brainstem (Fig. 1J). At 14 years of age, physical descriptions of large ears, deep-set eyes, and a wide-based gait were recorded, but no photographs were taken (the parents did not consent to facial photographs). At 16 years of age, his body weight was 41.5 kg (−2.0 SD), his body height was 162.7 cm (−1.3 SD), and his head circumference was 51.8 cm (−3.2 SD). The T2/FLAIR high-intensity lesion on MRI gradually decreased (Fig. 1E–H).

After written informed consent was obtained from the parents, whole-exome sequencing was performed on them and the
proband as previously described to determine the causative gene [4]. The examination protocols were approved by the Central Ethics Committee of Tohoku University School of Medicine Hospital (2018–2–216). The patient had a de novo heterozygous nonsense variant of the \textit{DYRK1A} gene, NM_001396.4: c.957C>G, p.Tyr319*. This was confirmed using Sanger sequencing (Supplementary Fig. 1). This variant is novel, but the same amino acid change (c.957C>A, p.Tyr319*) has previously been reported in \textit{DYRK1A}-related intellectual disability syndrome [5]. Based on the ACMG/AMP guidelines, this variant was rated as pathogenic [6].

Our patient’s clinical manifestations, consisting of physical and facial features as well as developmental and neuropsychiatric features, were compatible with the clinical manifestations observed in patients with \textit{DYRK1A}-related intellectual disability syndrome [1, 6, 7]. The prevalence of epilepsy without febrile seizure was 33% in a previous study involving 15 patients [8]. Table 1 shows previous epilepsy cases with \textit{DYRK1A}-related intellectual disability syndrome [7–9]. Regarding antiepileptic drugs, three cases were treated with valproate, and one case was treated with levetiracetam. As shown in Table 1, the EEG characteristics in these cases were unknown, and the seizure phenotypes of the two cases consisted of generalized seizures. As for the phenotype of the present case, the common seizure semiology of this disorder may be phenotyped as generalized seizures. The clinical course of epilepsy in patients with \textit{DYRK1A}-related intellectual disability syndrome may be well controlled [7].

Ventricular enlargement has already been reported in a patient with \textit{DYRK1A}-related intellectual disability syndrome [1, 9]. In follow-up MRIs of the present patient, the white matter lesions had slightly reduced signal intensity compared to the first image. Ji J et al. described similar white matter lesions as gliosis [1]. \textit{DYRK1A} has been noted to play an important role in neurogenesis, and white matter lesions in patients with pathogenic variants of \textit{DYRK1A} may arise during the early development of the brain. However, such white matter lesions can also be caused by other factors that are not known to be associated with this gene, such as inflammation, vascular abnormality, and infection. The pathogenesis of white matter lesions in patients with pathogenic \textit{DYRK1A} variants is unknown. The correlation between genotype and white matter abnormality is unknown in this disorder, and case with a different variant causing the same amino acid change did not show white matter abnormality [5].
### Table 1. Characteristics of epilepsy patients with DYRK1A-related intellectual disability syndrome.

| Patient 2 [7] | UMCN1 [8] | GF2852 [8] | .Moller et al. [9] | Present case |
|---------------|-----------|------------|-------------------|--------------|
| Genotype      | c.787C>T  | c.799C>T   | c.367C>T          | c.692G>A     |
| Gender        | F         | F          | M                 | M            |
| Age (year)    | 12        | 59         | 32                | 18           |
| Epilepsy onset age | 1 year | N.D         | 2-4 years         | 1 year       |
| Seizure semiology | Generalized tonic-clonic | Atonic and absences | N.D           | Generalized tonic-clonic |
| Seizure control | Well      | Well       | N.D               | Not tolerated |
| DQ/IQ         | N.D       | N.D        | N.D               | N.D          |
| MRI white matter abnormality | –        | N.D        | N.D               | –            |
| Meaningful words | +        | –          | +                 | –            |
| Height        | –2 SD     | < −2.5 SD  | −1.8 SD           | −1.5 SD      |
| Head          | −1.3 SD   | < −2.5 SD  | < −2.5 SD         | −3 SD        |
| Weight        | +1.7 SD   | + 2 SD     | −2.5 SD           | −3 SD        |
| Facial gestaut | +         | +          | +                 | +            |

F female, M male, N.D no data, AED antiepileptic drug, VPA valproate, LEV levetiracetam, DQ developmental quotient, IQ intellectual quotient, SD standard deviation.

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### Competing Interests

The authors declare no competing interests.

### ADDITIONAL INFORMATION

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