**A Novel Homozygous \( TBC1D24 \) Mutation Causing Multifocal Myoclonus With Cerebellar Involvement**

The phenotypic spectrum associated with recessive \( TBC1D24 \) mutations comprises focal epilepsy with cognitive impairment,\(^1,^2\) familial infantile myoclonic epilepsy without intellectual impairment,\(^3\) progressive encephalopathy with myoclonus and dystonia,\(^4\) progressive myoclonus epilepsy with ataxia,\(^5\) malignant migrating partial seizures of infancy,\(^6\) and DOORS syndrome.\(^7\) Here, we report on the case of a child with cortical myoclonus, cerebellar ataxia, and a novel \( TBC1D24 \) mutation.

**Case Report**

A 7-month-old boy born to a consanguineous Turkish couple had an acute episode of continuous myoclonus of the right hand lasting a few hours and mimicking epilepsia partialis continua. Interictal clinical evaluation, EEG, and MRI were normal. The boy, who is currently 8 years old, subsequently had attacks of myoclonus occurring once or twice a month, sometimes triggered by fever or fatigue. Myoclonic jerks alternatively affected the eyelids, either the right or left limbs, and sometimes the four extremities or the trunk. They lasted from several hours to up to 2 weeks, mostly disappearing during sleep, with consciousness preserved throughout. At 2 years of age, he had an episode of gait ataxia lasting several days and subsequently developed mild cerebellar syndrome. Mild intellectual disability became obvious after 5 years of age (Wechsler Preschool and Primary Scale of Intelligence at 6 years: verbal IQ: 55; performance IQ: 68; he was illiterate at 8 years old). The child did not respond to a number of antiepileptics, but topiramate gave a partial benefit.

Although interictal EEGs showed isolated spikes or bursts of spikes over bifrontal regions, paroxysmal anomalies were not found on ictal traces. However, video recordings with surface electromyography combined with accelerometry and EEG jerk-locked-back-averaging were taken together, highly suggestive of the cortical origin of myoclonus (Fig. 1A–C).

Cerebral MRI at 3 and 7 years of age showed progressive hemispheric (but not vermian) cerebellar atrophy with hypersignal of the cerebellar cortex and white matter on T2 and fluid-attenuated inversion recovery sequences (Fig. 1D,E). Single-nucleotide polymorphism analyses performed with the Human CytoSNP-12 kit (Illumina, San Diego, CA) in the patient and his healthy brother identified seven regions of loss of heterozygosity (LOH; \( >2 \text{ Mb} \)) present only in the patient. Sequencing of the \( TBC1D24 \) gene included in one LOH region revealed a homozygous c.809G\( \rightarrow \)A (p.Arg270His) mutation, present in a heterozygous state in his parents. This mutation is not reported in the homozygous state in public databases. In the ExAC Database, it is reported in two heterozygous carriers (allele frequency \( 1.6E^{-5} \)) and is predicted deleterious by Mutation Taster, polyphen-2 (score 0.992), and UMD predictor (Supporting Information).

Recessive mutations in \( TBC1D24 \) are associated with epilepsy with\(^3-^5,^7\) or without\(^1,^2,^6,^7\) myoclonus. Long-lasting myoclonus attacks were previously reported in two pedigrees with epilepsy and either normal cognition\(^4\) or severe encephalopathy.\(^1\) We report, for the first time, a patient with infantile-onset attacks of multifocal myoclonus that, despite their cortical origin, were not associated with other seizure types until 8 years of age. Cerebellar atrophy with hypersignal of the cerebellar cortex is a remarkable feature reported by two previous studies.\(^2,^7\) Brain imaging in other patients showed atrophy of cerebral hemispheres with\(^1\) or without\(^7\) cerebellar involvement. Our report confirms that \( TBC1D24 \) is responsible for cortical myoclonus and ataxia with cerebellar involvement.

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References


